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Editorial

Quantitative Morphology—A New Approach to Cardiac Pathology

GROSS PATHOLOGY is perhaps the last remaining field of medicine where quantitative methods have yet to penetrate. Nowhere is this obduracy more striking than in the cardiovascular field. While quantitative methods have led to literally thousands of articles in recent years on the energy and work of the heart, there have been barely a handful of contributions on its architecture. This is an astonishing discrepancy, for the physiology of the heart can never be separated from its geometry if we are ever fully to understand cardiac function and dysfunction.

It is not difficult to see why quantitative methods have been slow to appear in gross pathology. By virtue of their research interests pathologists have moved in a direction opposite to that of the gross morphologist, turning to microscopic methods of study as exciting new discoveries in ultrastructure and histochemistry have unfolded. Furthermore, the classical methods for dissection that pathologists are taught couldn't be more skilfully contrived to defeat an interest in morphology. At postmortem examination, the pathologist incises and flattens the heart, reducing it from a three-dimensional structure to a two-dimensional mass, destroying its functional geometry. As a result, questions arising among physiologists and clinicians regarding heart function that relate to the structure of the heart cannot be answered by the pathologist, leaving a serious informational and professional gap in cardiac research.

But there is perhaps still another reason why a quantitative approach to pathology has been slow to appear: the mathematical tools are often unfamiliar ones. In other branches of medicine quantitative methods usually involve what may be called one-dimensional manipulations, simple arithmetic operations with integers. But morphology is a three-dimensional problem and requires different tools: for example, transforms in a three-axis coordinate figure to "uncoil" the twist of the pulmonary artery and aorta in order to prove whether or not there is such an entity as partial transposition of the great vessels, or three-dimensional descriptive geometry to calculate the angle between inflow and outflow tracts from biplane angiocardiograms, or vector analysis to study the distribution of fiber shortening in various parts of the wall of the cone-shaped left ventricle.

One mathematical tool that is of interest to the cardiac morphologist and a newcomer to medical research is topology. In contrast with the mathematics of integers, this is the mathematics of surfaces, and it is relevant to cardiac pathology because the essence of any pump is its surfaces. Figure 1 illustrates one simple way in which the circulation can be studied topologically. In this instance we consider the entire cardiovascular system—heart and blood vessels—to consist of two systems, one arterial and the other venous, and con-

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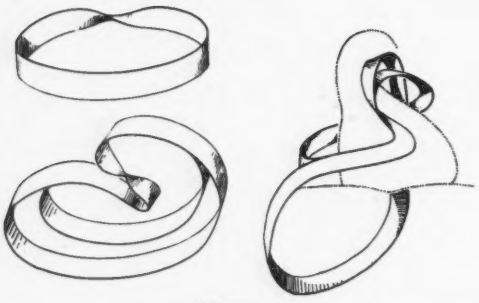

Figure 1

Diagrammatic representation of topology of circulation.

struct the "surface" that separates them. When we trace this surface through the body and the heart (where the surface represents the atrial and ventricular septa and the plane tangential to both the pulmonary artery and the aorta), we have the construct on the right of figure 1. Interestingly enough, this proves to be what the topologist calls a "single surface," the simplest of all topologic surfaces, classically represented by the "Moebius ring" illustrated on the upper left of this figure. A single surface is one where all points on its surface can be reached without crossing an edge. This proves to be the case for the circulation viewed in this way. To be sure, in the drawing on the right, one arc of the Moebius ring is split morphologically to allow for the anatomic fact that when a red cell travels on the inner surface of this part of the ring it is traversing the pulmonary circuit, and is in a different part of the body than when it is on the outer surface of this part of the ring traveling to all points of the systemic circulation. The "twist" that allows this to be a single surface like the Moebius ring is accomplished by the spiraling of the truncal septum, which divides the truncus arteriosus into a pulmonary artery and aorta. But this is a "twist" only to the anatomist, not to the topologist. And herein lies one of the powers of mathematics, for it is the one language that can liberate us from the rigidities of what the anatomist and pathologist "see," when it is useful to be liberated. The fact that the entire circulation can be reduced to the simplest of all topologic forms—the single surface—is a potentially interesting operation, for progress often depends upon reducing an intrinsically complex problem to its simplest quantitative form.

I think it was Henry James who insisted that man's greatest invention was not the wheel but the simple declarative sentence. Whatever merits Henry James' notion has philosophically, it has none scientifically. For it was the simple declarative sentence that delayed for so many centuries the development of a much more powerful language, mathematics, a language that even today is a foreign tongue for most of us. The declarative sentence may be superb for expressing internal, semi-rational moods and perceptions, but it is a weak and limited tool for describing the world around us. It is a linear, one-dimensional language that cannot handle simultaneous relationships, it is cumbersome with quantitative information, and only in the licensed ambiguities of poetry can it deal with transients, dynamic states, and variables —and then only with appalling, however beautiful, imprecision. Perhaps it is true that society could not have survived were it not for the rich reservoir of ambiguity in our spoken language. Nevertheless, it was the strong grip of this language that so long delayed the progress we have witnessed during the past hundred years in medicine, a progress that has at its foundation the adapting of quantitative language to medical problems. The strong grip is still to be seen in gross pathology. The usual description of the heart in a medical article reads more like a Baedeker travel guide than a piece of scientific literature, as we are toured from valve to valve, from one chamber to another.

Many years ago Kant pointed out in connection with chemistry that a discipline can be said to approach a science only insofar as it relates to mathematics. During the past decade a series of papers has been emanating from Western Germany illustrating the use of mathematical methods in the study of cardiac morphology. Linzbach and his colleague Hort in Gottingen, Schoenmakers in

Dusseldorf, and others have used these tools to shed important new light on such problems as cardiac hypertrophy,[1, 2] the mechanism of cardiac dilatation,[3] and many other problems that in American laboratories have reached an impasse, a sort of scientific supererogation, because our focus has been so exclusively physiologic.

The new approach is called "quantitative morphology," and while its usefulness for cardiovascular research is obvious, it is also applicable to many other fields of investigation. For example, the geometry of the pulmonary alveolus, the morphology of the cellular proliferation of cancer, and the spatial relationships of cerebral ganglion cells—all of which have been studied descriptively, when they are quantified, open important new understanding in their respective fields.

Quantitative morphology is not a new approach in science. The brilliant Oxford naturalist-philosopher d'Arcy Thompson was perhaps its father for modern times. His fascinating two-volume work *Growth and Form* was first published in 1914. In it he used simple mathematical tools to approach such age-old questions as why leaves have their particular shapes, what governs the pattern of the tines of the reindeer's horn and the symmetric convolutions of sea shells, why are the legs of an insect so thread-like while those of the elephant so much more massive relative to body size, what physical problems are involved in the one-legged stance of the crane, and the shape of a sea gull. But long before d'Arcy Thompson, Galileo expressed the morphologist's point of view when he observed "while you may often see a dog ride on another dog's back, you will never see a horse ride on another horse's back," and pointed out the reason: mass increases as the square of linear length, and an animal twice the size of another is four times more bulky. The language of quantitative morphology is mathematics, and it can be expected that the development of quantitative methods for studying cardiac anatomy and gross pathology will bring important new concepts and tools for unraveling basic problems of heart function in health and disease.

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The Gold in Useless Knowledge

Discussion of the value of basic research is as pertinent today as it was when Faraday, queried about the usefulness of his discovery of electric induction, countered with the question, "Of what use is a newborn baby?"—WENDELL M. STANLEY, Editorial, *Science*, March 2, 1956.

Emotional Factors in Coronary Heart Disease

By HOWARD B. SPRAGUE, M.D.

ANYONE intrepid enough to discuss the role of the emotions in coronary disease exposes himself to stresses that are asserted by some to be lethal. Thus, when I essayed, Canute-like, a few years ago, to challenge the concept that Western civilization is inevitably emotionally bad for the coronaries, I was told, in print,[1] that it was "almost incredible" that I should have considered the terrors of grief, war, suicide, manic depressive insanity, and horrendous primitive taboos (stresses under which man has always suffered) as approaching in deadliness the hazards of our socioeconomic existence; and this in spite of the assertion by other psychosomaticists that fear, anger, resentment, frustration, and depression produce a greater cardiac output for a longer time than standard exercise. Naturally this social disapproval, this failure on my part to be "agin Sin," has been very hard on me.

My friend, Dr. Louis Katz, has rightly said, concerning this matter of the emotions in atherosclerosis, ". . . too much has been said on this subject on too little evidence. We should do more research and less talking!" However, he stated that the Committee on Emotions and Cardiovascular Disease of the Chicago Heart Association has proposed that it devote 2 years to exploring the field, through a series of conferences, to decide whether or not even to undertake a major study of it.[2] I predict that the Committee will decide in the negative, but, at any rate, they must still be in the talking stage and will perhaps allow me a word at this meeting. Dr. Katz has admirably outlined the many questions needing answers.

What, I think, is the difference between the two major schools in this clouded area is really the emphasis upon the relative influence of heredity and of environment, which we all recognize cannot be treated separately. As Hogben says, "no statement about a genetic difference is clear, unless it includes or implies a specification of the environment in which it manifests itself in a particular manner." And in referring to the "Nurture" versus the "Nature" point of view, he says that the former justifies its position by "arguments which suggest that caterpillars of the cabbage butterfly will take to a mixture of pollen and honey. Their opponents appear to hold that Newton would have written his Principia if he had been born in Tasmania."[3]

The whole concept of causation is, after all, a weighty business and in the obviously polygenic etiology of coronary atherosclerosis and occlusion one must almost admit the legal definition of cause as phrased in the Workmen's Compensation Act of New Zealand: "Affirmative finding is not justified because it is possible, or even probable, that the disease was so caused, accelerated or aggravated; but it must be the result of a legitimate inference from the proved and admitted facts."

My inclination is toward the role of inborn errors of metabolism as preponderant over the influences of environment. Were we to capture that will-o-the-wisp, a satisfactory test to define *individual* liability to coronary disease, I venture to say that the nonsusceptibles could eat what they wished, work as they wished, and indulge in any of the more appealing vices without cardiovascular retribution.

It seems obvious that much energy is being needlessly channeled into the demonstration that emotional stimuli have an effect upon serum lipids. As Page has shown, studies have been presented indicating that the emotions raise, lower, or leave unaffected the serum cholesterol. There are large individual variations and more work is needed in determining normal levels over long periods of time. This

The G. Lyman Duff Memorial Lecture, delivered October 20, 1960, at the Fourteenth Annual Meeting of the American Society for the Study of Arteriosclerosis. St. Louis, Missouri.

response, like that of other serum lipids, blood sugar, coagulability and fibrinolysis, or blood pressure, is part of the normal balancing of homeostasis; and it is not at all clear that any of these measure an individual liability to coronary atheroma or thrombosis. Pituitary-adrenal or other hormonal effects upon these, or upon local arterial reactions, are similarly obscure.

Dr. Forrest E. Kendall, in inviting me to present the Duff Lecture, emphasized the clinical aspect of my discussion and I am not attempting to review the literature of the biochemical and central nervous system effects of emotional factors upon the circulation. It is perhaps sufficient to point out that there exists an idiosyncratic, stereotypic reaction to mental stress in each one of us, which I doubt very much is predictable by any presently available test or "profile." Secondly, if some normal constituent of the blood is altered by stress, the chances are that the alteration is "good" for the organism, rather than "bad." Originating, as it does in the phylogenetically oldest part of the cerebral cortex, it must have had some survival value. I say this even facing the criticism of my naive teleology.

Thirdly, it has recently been shown that when persons with high scores in tests for maladjustment or anxiety were retested, their maladjustment or anxiety scores were lower the second time. As the editorial comment on this states ". . . merely repeat the test and do nothing else, and the disorder, at least as measured by the test, will improve!"[4]

Attempts to define the coronary-prone patients on the basis of the emotional reactions of known coronary patients compared with so-called "controls" of so-called "normal" individuals seem to me unrealistic. Those reported appear not to have considered somatotype as related to its common temperamental component, nor racial differences relative to overt hyperreactivity to irritation. Certainly my patients with coronary artery disease do not conform so beautifully to what has been called the Hollywood concept of the American business man. Of course if some objective screening device on the emotional level were available, the method could test all individuals of an occupational class and discover the hyperreactors, and such could be followed to see if they developed overt coronary disease more often than others. The trouble is that "stress cannot be defined by the dimension of the load."

An aspect of this problem seems to have been disregarded and to which I would like to summon you. It is commonplace for us, as clinicians, to have patients, or their wives, describe a stressful situation in which the first symptoms of coronary occlusion developed. Similarly, as students, we were taught by Richard Cabot that a patient with an acute illness could always remember something that he had eaten that must have precipitated his attack. I will grant that there are relationships, at least temporal, between some attacks of myocardial infarction, or the first appearance of angina, and a specific event, an event that may have revealed the underlying coronary disease earlier than it might otherwise have shown itself. Aarons recently found only two such claims attributed to exciting arguments in a series of 100 insurance cases with fatal heart attacks. But what I am referring to is not the alleged precipitating event, but rather the theory of prolonged or severe emotional tension, existing for weeks or months before the coronary occlusion as of great etiologic significance.

There does not seem to be much question but that at least 50 per cent of the men in this country have significant coronary pathology by the age of 50 and that we are all exposed to mental stress. For the sake of argument, let us attribute the downfall of the coronary patient to his job stress or what has been called the "general forms of socioeconomic stress unique to Western societies." In this connection let me quote from Parkinson's book "The Law and the Profits" the items of a bill rendered to an Englishman by a tax consultant as follows: "To enable you to evade the income tax payment, a laborious and intricate work, your accounts extending over a period of fifteen months, £6.6.0." The antiquity of these supposedly lethal socio-

economic stresses is demonstrated by the fact that this bill was rendered in 1852, 108 years ago, and long before anyone ever heard of a coronary thrombosis. One wonders if the tax consultants of a hundred years ago had seasonal rises of serum cholesterol and shortened coagulation times or, as Gofman has shown, if they, like so many others, eat more under stress to account for a bit of a rise in blood lipids.

But the point I wish to make is that even if the dominating role of the emotions in atherogenesis or short clotting time is assumed, why is it that continuation of such stresses or even increase in them fails to result in another coronary thrombosis in an impressive number of patients?

The physician by his special brand of necromancy may be credited with protecting his patient from further destruction, be it through advising business adjustments, exercise, low-fat diets, polyethenoic fats, or anticoagulants, but if he is reasonably honest, he will recall men who disregarded all his advice and lived merrily on, in spite of the direst of predictions.

In my own experience, it seems to me that the man who recovers from a myocardial infarct sufficiently well to return to his usual work does best if he stops smoking, reduces weight, and increases his physical activity. Indeed, ability to follow such a regimen, I use as a test of his real motivation to get well. But since I am encouraged to be clinical, let me give you a few examples:

1. A building and road contractor of 44, first seen in 1949, who "said he had been working out of business grief" for 4 to 5 years, had vague chest pain for 6 years thereafter until he had a myocardial infarct in 1955. This attack, however, although it was preceded by hard work getting contracts, came after a New Year's Eve party lasting to 4 A.M., during which he consumed much liquor and smoked excessively. A similar one occurred New Year's day with a party continuing to 2:30 A.M., and the enjoyment of his son's wedding the following day. The directions to stop tobacco, and lose weight (now 15 pounds), and to play golf were followed. A fiery man, who screamed over the telephone and broke his golf clubs when he got a poor shot, he now admits that he merely says "Dear, Dear" when he slices into the rough. However, his business pressures are still heavy, he has suffered the collapse of a secondary investment venture in Vermont, and he is in the midst of financing a new experimental invention with a turmoil of banks, SEC registration, and stockholders meetings. He could perhaps represent the behavior pattern of the tense executive alleged to be susceptible to coronary disease, but he is mesomorphic, and was overweight and a heavy smoker. Stress, however, is still a factor in his life, yet he feels fine and has a normal electrocardiogram.

2. An insurance executive of 47 was first seen in 1951 in the hospital with a posterior myocardial infarct. He is an extremely hard driver in his business, having a very profitable insurance general agency. After his recovery, he returned to his strenuous competitive career. His weight, which he had reduced to 156, has risen in 9 years to 182, but from a consumption of 60 cigarettes a day he abruptly reduced to zero. This man has no interest in anything but work, which he says never tires him. He overdoes in food, liquor, business, and long trips. He adds more work, opens new companies, and insists on having two Cadillacs, runs a variable mild hypertension, has gout and polycythemia, and gets very little exercise. He has grieved at the loss of a grandchild and worries about his wife's hysterectomy and her continual complaint that he is antisocial, but he has no symptoms. What has protected him for 9 years from the dire effects of stress?

3. Twelve years ago I saw a 46-year-old sales engineer for a large machinery manufacturing firm and was uncertain about the cause of his bizarre chest pain, but 2 years later he had a severe myocardial infarct. A tense situation had existed in the office and he had felt better when on the road inspecting the engineering work. He had been a two-pack-a-day smoker, and liquor had at times been victori-

ous. After recovery it was thought wise to confine him to office work where he was exposed to a boss who was addicted to the Martini lunch pattern, and who held his liquor poorly. The patient also hates telephones and crowds and is generally frustrated. Four years after his attack his wife, whom he adored, died lingeringly of metastatic cancer of the brain following a breast operation and craniotomy the year before. A year later he remarried a much younger woman who does not fit his pattern of marriage successfully. His weight originally was 165 to 170 and is now 155. He smokes a pipe, but no cigarettes. Two years ago his 14-year-old son was killed in a friendly tag football game. This man appears pale and tired and has some angina with effort, but works steadily. After 10 years of emotional agony, he has the electrocardiographic signs of his old infarct, but normal blood pressure, good heart sounds, and no cardiac enlargement. Why does he not clot fatally?

4. Almost 11 years ago, a 49-year-old man in the amusement business was seen by me in an emergency at home in the throes of a severe myocardial infarct. He had had no symptoms until 5 days before, when he had had substernal pain during coitus. He had been under no unusual chronic or acute stress in business prior to the attack, and is a quiet, rather gentle sort of man.

He made a good recovery. His weight, which in 1952 was 160, is now 147; cigarette smoking, which was heavy, has stopped completely. Golf, which he played rarely, he now contrives to play most of the year, at home or in Florida. He returned to work at full time, but during all these years he has also been very active in the behind-the-scenes politics of Massachusetts, gambles at the races, has had horses of his own, and has survived his nervous wife's menopause. At times he has mild angina.

In the past 3 years he has been much disturbed by business, politics, and family troubles. His daughter had a miscarriage, his daughter-in-law left a child in a car and the child released the brakes, allowing the car to go over a bank; he lost $5,000 betting on his own horse; he put a large amount of his money into the campaign of the surprise loser for position as Mayor of Boston; the winning opponent has destroyed his business; and in December 1959 his beloved daughter died in childbirth. While some of this man's stresses are not those peculiar to Western civilization, I must confess that I wonder, if the emotions are so atherogenic or thrombophilic, why this man has had no further coronary attack in 10 years. What indeed was the cholesterol, and clotting time, and fibrinolytic activity of Job? We know only that he survived his tribulations, regained his prosperity by Godliness, and lived for 140 years.

It is standard operating procedure in discussions of this sort for the opposing forces to belabor each other with references from the literature—a sort of Battle of the Bibliographies, the weight of shot and shell being measured by volume and caliber of the authors. I am no exception, but shall attempt to place a few bulls'-eyes, and not resort to saturation bombing.

I note that Dr. Harry J. Johnson, President of the Life Extension Foundation, in the August 22, 1960, issue of *U. S. News and World Report* was interviewed on the subject of "How to Work Harder and Stay Healthy." His answers were based on an examination by his agency of about 20,000 executives a year. Here are a few quotations: "there is no particular health hazard to the job of being an executive. Any health hazard is the result of his routine of living outside the office."

"Quite often the healthiest fellows were those who put in the longest days and did the hardest work."

Question: "Did the business men in your survey say they were tense during the day? Did they list this as a problem?"

Answer: "No. We were amazed again to find in this study that there were just 13.3 per cent of executives who stated they felt they were under undue or constant tension; 87 per cent stated they were under some pressure, but it didn't bother them particularly. It was part of their job and they rather enjoyed it."

"I don't believe we have any higher percentage of people suffering from excessive tension among executives than in any other group of workers." "They do not have a corner on ulcers, or coronary heart disease." "The man who needs most looking after is the assistant vice-president."

"We're not convinced that tension plays a very important part as a cause of heart disease. We find heart disease in people whose jobs are quite free of tension-producing situations in about the same proportion as we find in the others."

Moving to the other end of the spectrum of masculine motivation, we find McCullagh and Lewis reporting on a study of Trappist monks.[5]

I am not prepared to prove anything about the emotional status of Trappist monks. Psychiatrists say they don't even have normal safety valves. For all I know, they may grind their teeth, or clench their hands, when exposed to psychological tests, but certainly the accepted image of the monk is as noted in an editorial in the *New England Journal of Medicine,* [emotional tension] "should hardly be compatible with what is obviously a life of contemplation, removed from the ordinary stresses of existence."

But the study shows that, while the Trappists have relatively low blood cholesterol levels, they have not been spared from arteriosclerosis or arterial hypertension; in fact "the data suggest that arterial hypertension is more frequent in them than in other men of the same age in the American population generally." All this, I may add, in spite of a lifetime of "placidity, frugality, and abstinence from all animal foods, except milk and very small amounts of cheese." They do indulge in daily excercise and the figures suggest to me that they live longer than the average.

From a report by Barnes, Ratzenhofer, and Tacherne,[6] we learn that a review of 24,546 autopsies shows that seven times as many heart attacks occurred in Graz, Austria, in 1958 as in 1944 and 1945, and they say "it is hard to imagine more stress at any time than during the War and the occupation of Austria." I agree, even though some implicate the unique socioeconomic stress of Western man, and gaily dismiss the stresses of flood, famine, and pestilence and war by saying that they are not significant, since these are "outside the individual's control" and "since in all forms of group emotional stress, such as war, the individual's stress is either submerged or lost." What happens to individual stress when it is "submerged"?

In any event, the paper by Stewart[7] that is quoted in this connection is, after all, from a British pen describing a social system toward which we are tending, but have not reached; a system that he says contains the "tattered survivors of the former 'middle classes' ". The Chicago studies show incidence rates of coronary heart disease to be high in all strata of the middle-aged male population of the United States.[8]

I have referred to the genetic determinant of atherosclerosis and it is evident in some degree in familial hyperlipemic states. It may be some fault in enzyme systems possibly linked with a peculiar somatic or psychic pattern. Fortunately, we are all heterozygous for most of our genetic inheritance, making us, as higher mammals, very difficult to quantitate. In pure strains of mice, in which the history of the inheritance may approximate 1,000 years of human life, certain traits may emerge. For example, in two such strains the individuals of one race, when given the choice of a beverage of pure water or dilute alcohol, will invariably choose the alcohol. Were one to suppose compulsive drinking of this sort, in the absence of the knowledge of racial influence, to be based on emotional stress, one might attempt a complex psychological testing to explain it. The reason these mice drink alcohol is that it is offered to them. Similarly, I believe that the human male develops atherosclerosis, or coagulation-fibrinolysin imbalance, if the genetic factor is present and the environment of diet, tobacco, physical inertia, plus long hours of work, or other things, perhaps forced on him by socioeconomic stress, are operative. As Dr. Stewart Wolf[9]

says, "It may be that the mechanics that govern the concentration of serum lipid are brought into play in the face of demand for effort that is figurative as well as literal. The possibility that any such changes are actually related to the mechanisms of coronary atherosclerosis is entirely speculative."

Coronary disease is ubiquitous. It is too nonspecific in its targets to be the result of a single cause. Indeed, it appears to be present wherever the livers of a population are in good order. The Chicago study[8] of a utility company shows "virtually no sub-group differences in serum cholesterol levels of white males" on the basis of socioeconomic growth. Raffle,[10] in England, in a study of coronary disease in bus drivers and the population generally, reports, "the epidemological evidence that stress is a factor in disease is, at best, tenuous."

It is fair to ask why I am disturbed about the categorical attribution of coronary disease and thrombosis to emotional factors. I have a few reasons:

In the first place, it is so easy and popular. The American public is constantly fed with anxiety about its stresses. It is encouraged to demand security from all sorts of worry. The result is that certain occupations are becoming classified as stressful, and therefore special legal perquisites are demanded as compensation for being a fireman, a policeman, or a politician. Doctors go into court and testify that it was obvious this or that man's job was the real cause of his coronary thrombosis. Laws are passed which inhibit the employment of older workers, and lawyers have a field day. It seems to me that this is evidence of decadence. It certainly is not in the pioneering tradition. But I suppose few of us can be pioneers nowadays.

Secondly, the tendency to consider emotional stress as confined to socioeconomic tension seems to me untenable. Engel[11] writing recently on "A Unified Concept of Health and Disease" lists the four "factors that strain current capacities of the organism."

"1. Factors which injure by virtue of physical and/or chemical properties.

"2. Physical factors that lead to injury when insufficient or unavailable.

[He refers here to the essential chemical elements—oxygen, water, electrolytes, etc.—that the organism must obtain from the environment (deficiency states), and the essential substances formed in the body (e.g., hormones): insufficiency states.]

"3. Microorganisms—parasites.

"4. Psychological stress."

"Highly individual factors will determine what particular situation or process will constitute a psychological stress for any particular individual. Nonetheless, experience permits us to recognize certain categories of phenomena as being the main means whereby psychological stress may come about."

"a. One is the loss of psychic objects (as represented by persons, ideals, valued possessions, job, body function and image, social roles, goals, home, country, etc.)."

"Grief or mourning represents the most familiar response."

"b. Injury to the body—infliction of pain, mutilation, etc., actual or threatened, is a prominent source of psychologic stress."

"c. Frustration of drives."

What I have attempted to illustrate is that, in known victims who have recovered from myocardial infarction, the continuation of stress or even its exacerbation, often does not result in an acceleration of demonstrable atherogenesis or coronary occlusion. It may of course be possible that correction of some other factor negates the effect of the emotions.

Harold Dorn[12] has well said "To unravel the tangled skein of causation of disease by the observation of man in his environment requires the utmost persistence, a profound skepticism of the obvious, an alertness for selective factors that have produced the most readily available subjects for study, the ability to penetrate beneath the surface of the observations, a strong distrust of what is said or seen since the unchecked human memory is probably the most unreliable research instrument in existence and a willingness to spend long hours upon the development and perfection of methods of making observations

coupled with the patience to await the occurrence of the succession of events most relevant to the hypotheses to be tested." This latter phrase I find most wise and cautionary.

I can only hope that coronary disease will turn out to be more amenable to changes in the environment other than repeal of the Industrial Revolution or a return to the alleged mental stability and placidity of a rigid stratified society. For as Rene Dubos says,[13] "To grow in the midst of dangers is the fate of the human race, because it is the law of the spirit."

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On Permanent Patency of the Mouth of the Aorta, or Inadequacy of the Aortic Valves

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Diagnosis.—Inadequacy of the aortic valves may be confounded with narrowing of the mouth of the aorta, either congenital or from diseased valves, with disease of the auriculoventricular valves, with aneurism of the arch of the aorta or *arteria innominata,* with nervous palpitations, and with asthma . . . The visible pulsation of the arteries, arising from the arch of the aorta, which forms so striking a sign of inadequacy of the aortic valves, is wanting in narrowing of the mouth of the aorta. The pulse also is strikingly different in the two diseases. In narrowing of the aortic orifice it is small and contracted; in inadequacy of the aortic valves it is invariably full and swelling. In narrowing of the aortic orifice there is generally a marked contrast between the pulse and the impulse of the heart. The pulse is small and contracted; the impulse of the heart is strong and energetic.

"Nonspecific" ST and T-Wave Changes

By CHARLES K. FRIEDBERG, M.D., AND ALBERT ZAGER, M.D.

ONE of the commonest problems in electrocardiography is the interpretation of ST-segment depression and T-wave inversion without other characteristic changes, particularly when there is clinical uncertainty regarding the presence and nature of an acute coronary attack. A common solution, often unsatisfactory to the clinician receiving the report, is the statement "The ST-segment and T-wave changes are nonspecific abnormalities." A careful analysis of the degree of ST depression and character and depth of inversion of the T waves and a correlation of these findings with clinical conditions may enable us to arrive at a more definite electrocardiographic diagnosis. Since no such systematic analysis has been reported, this study was undertaken.

Method

The electrocardiograms of 1,000 consecutive adult in-patients interpreted by the members of the cardiology staff of The Mount Sinai Hospital, were reviewed and correlated with the clinical status of the patients.

The findings are representative of records of a large, voluntary metropolitan hospital. The adult patients were from both the ward and private medical and surgical services during a period of approximately 4 months. Although usually the records were taken for specific clinical indications, some represented routine preoperative electrocardiograms in the elderly age group. Records that primarily involved abnormalities in rhythm were excluded from the study.

The abnormal electrocardiograms were classified into the following groups: acute and healed transmural myocardial infarction; bundle-branch block; ventricular hypertrophy; pericarditis. There remained a large abnormal group that did not satisfy recognized criteria for any of the above groups, with changes that were designated nonspecific ST-segment and T-wave abnormalities.

The *depth* of ST-segment depression and of T-wave inversion was contrasted in those patients who had no recent cardiac pain, in those who had pain of less than one-half hour duration and in those who had pain of longer duration. The frequency with which isolated T-wave abnormalities, isolated ST-segment abnormalities, or combined abnormalities occurred in the various categories was also analyzed.

A similar analysis was made relating abnormalities in *contour* of the ST segment and T waves in the same groups of patients. The recorded depth of T-wave inversion or ST-segment depression was the maximum change in precordial leads V_3 to V_6. Tracings considered to have abnormal contour of the ST segment exhibited an upward convexity of the ST segment or a long, straightened or downward sloping ST segment. The term "ischemic T wave" in this paper included both the "coronary T wave" of Pardee,[1] which is a downward sharply peaked T wave with symmetrical limbs following an upward convexity of the R-T interval and the "cove plane" T wave of Oppenheimer, Rothchild, and Mann[2] with a curved descending limb, peaked apex, and straight ascending limb.

Results

Of the study group of 1,000 electrocardiograms there were normal findings in 590 and abnormal in 410 cases. The abnormal ones were subdivided into 93 cases of acute transmural myocardial infarction, 63 cases of healed myocardial infarction, 24 cases of bundle-branch block, 18 cases of ventricular hypertrophy, three cases of pericarditis and 209 cases in which the ST-segment and T-wave changes were nonspecific abnormalities (table 1).

In the latter group of 209 patients with nonspecific ST-segment and T-wave changes, 46 were receiving digitalis, 22 had recent cardiac pain of less than ½ hour duration, 35 patients had recent cardiac pain of ½ hour or longer in duration (table 2). Twenty additional patients had had recent cardiac pain ½ hour or longer but were already included in the previous categories because they had received digitalis or had other causes for ST-segment and T-wave abnormalities

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Table 1

Analysis of 1,000 Consecutive Adult Electrocardiograms

Normal	590
Abnormal	410
Total	1000
Analysis of Electrocardiographic Abnormalities	
Acute infarct	93
Old infarct	63
Bilateral B.B.B.	1
R.B.B.B.	17
L.B.B.B.	6
R.V.H.	1
L.V.H.	17
Pericarditis	3
Nonspecific ST and T changes	209
Total	410

B.B.B. = Bundle branch block; R.V.H. = Right ventricular hypertrophy; L.V.H. = Left ventricular hypertrophy.

listed in table 1. One-half hour of cardiac pain was selected as the dividing point in an effort to distinguish patients with angina pectoris from those in whom the cardiac pain might be associated with myocardial necrosis.

The remaining 106 patients with electrocardiographic ST-segment and T-wave changes had had no digitalis therapy or recent cardiac pain, and the electrocardiographic abnormalities did not satisfy the criteria for any specific abnormality. By correlation with the clinical histories a possible etiology for the ST-segment and for T-wave changes was uncovered in 57 of these 106 patients (table 3).

Clinical Correlation with Depth of ST-Depression and T-wave Inversion

In the group of patients with no apparent explanation for the ST-segment and T-wave changes, 84 per cent had less than 0.5 mm. of ST-segment depression and less than 1 mm. of T-wave inversion; only 32 per cent of the group for whom there was a postulated explanation had such minimal changes (table 4).

Frequency of Combined and Isolated ST and T-wave Changes

In the patients with recent cardiac pain of ½ hour or longer duration, 11.4 per cent of the electrocardiograms were classified as

Table 2

Clinical Analysis of 209 Cases with Nonspecific ST-segment or T-wave Changes

Digitalis therapy	46
Recent cardiac pain ½ hour or longer	35
Recent cardiac pain less than ½ hour	22
No recent cardiac pain	106
Total	209

abnormal solely on the basis of T-wave inversion (table 5); in the group with recent cardiac pain of less than one-half hour, 4.6 per cent were classified as abnormal on this basis. By contrast, of the patients with no recent cardiac pain 42 per cent were classified as abnormal, solely because of T-wave inversion.

Depth of T-wave Inversion and ST-Segment Depression

The depth of T-wave inversion was 2 mm. or more in 10 (28.6 per cent) of the 35 cases with recent cardiac pain lasting ½ hour or longer, in 11 (50 per cent) of 22 cases with recent cardiac pain for less than ½ hour, and in only 12 (11 per cent) of the 106 cases without recent cardiac pain (table 6). A clinical review of the 12 patients with T-wave inversion of 2 mm. or greater, but no history of recent cardiac pain disclosed that six patients had blood pressures of 170/90 or above, two had abnormal serum electrolytes, one had central nervous system disease, two had postoperative shock, and one arteriosclerotic heart disease.

The depth of ST-segment depression was also studied in relation to the same clinical groups (table 7). T-wave inversion between ¾ and 2 mm. in depth did not appear to be significantly different in the groups with or without recent cardiac pain. Recent cardiac pain had been present in all 10 patients with electrocardiographic ST-segment depressions of more than 2 mm. ST-segment depression exceeding 0.5 mm., but less than 2 mm. occurred much more frequently in patients with recent cardiac pain than in those without such pain. There were only 14 among the 106 patients in the category with "no recent

Table 3

Possible Etiologies of One-Hundred and Six Cases with Nonspecific ST and T-Wave Abnormalities

	No known cause	ASHD	HBP 170/90 by history	HBP and ASHD	Anemia	Pulmonary embolus	CNS disease	Post-op. shock	Clinical pericarditis	Clinical cor pulmonale	Rheumatic valvular	Electrolytes	Total
T	25	2	6	1	2	1	4	2	1	0	1	0	45
ST and T	19	4	6	2	0	2	5	0	2	2	4	2	48
ST	5	2	2	2	0	0	1	1	0	0	0	0	13
Totals	49	8	14	5	2	3	10	3	3	2	5	2	106

ASHD, Arteriosclerotic (coronary) heart disease; HBP, hypertension; CNS, central nervous system.

cardiac pain" with ST depression greater than 0.5 mm. Three of these patients had a blood pressure of 170/90 or more, four had clinical arteriosclerotic (coronary) heart disease, one had thyrotoxic heart disease, one had abnormal serum electrolytes, two had severe cerebral disease, one had sprue with normal serum electrolytes, and two had no clinical heart disease but were over 80 years of age.

Ischemic ST Segment and Ischemic T Waves

The clinical groups with and without cardiac pain were correlated with the presence of the ischemic type of ST segment and ischemic T wave (table 8). There was no significant difference in frequency of the ischemic contour of the ST segment among the three groups. On the other hand, there was a definitely higher incidence of ischemic type of T wave in the groups with recent cardiac pain than in those without pain, and the difference was even greater in terms of the combination of ischemic ST segment and ischemic T wave.

Discussion

Of the 410 abnormal electrocardiograms more than 50 per cent were reported as showing nonspecific ST-segment or T-wave abnormalities. The 209 cases in the latter category, when correlated with the clinical history fell into four groups:

1. Forty-six (22 per cent) had received digitalis, which could account for the ST-T changes;

2. Forty-nine (24 per cent) had no apparent cause for the ST-T abnormalities.

3. Fifty-seven (27 per cent) had an acute episode of cardiac pain within 5 days prior to the electrocardiogram; the pain lasted a half-hour or longer in 35 and less than ½ hour in 22;

4. Fifty-seven (27 per cent) had no recent cardiac pain but suffered from some disease that could be regarded as a possible cause for the electrocardiographic changes.

A consideration of these groups suggests an approach to a more definite diagnosis than "nonspecific ST and T-wave abnormalities." It seems desirable first to determine whether the patient has been receiving digitalis. Although characteristic ST-T-wave changes have been described following digitalis the changes are not always characteristic.

If digitalis is excluded as the cause of electrocardiographic changes, the problem is to determine whether the ST-T changes developed in connection with recent cardiac pain and may therefore indicate myocardial ischemia or necrosis. If there is no history of a recent acute attack of cardiac pain, it is necessary to distinguish between ST and T-wave changes due to some competent clinical cause (other than acute myocardial ischemia or necrosis) and ST and T-wave changes that are of no clinical significance. This study has indicated that such differentiation can almost always be made on the basis of the clinical history and the observation that the combination of ST-segment depression of less than

Table 4

Contrast of ST-Segment Depression or T-Wave Inversion in Group with No Apparent Explanation and Group with Possible Explanation for Abnormalities

	Insignificant ST and T changes*		ST depression and T inversion†		Isolated T inversion more than 1 mm.		Isolated ST depression more than ½ mm.		Total
	No.	%	No.	%	No.	%	No.	%	
Apparent explanation	18	32	20	35	16	28	3	5	57
No apparent explanation	41	83.7	0	0	7	14.3	1	2	49

*ST depression less than 0.5 mm.; T flat or inverted less than 1 mm.
†ST depressed more than 0.5 mm.; T inverted more than 1 mm.

Table 5

Classification Based on Isolated T-Wave Inversion, ST-Segment Depression, or Combined T-Wave Inversion and ST-Segment Depression

	Both ST and T abnormalities		Only T-wave inversion		Only ST segment depression		Total
	No.	%	No.	%	No.	%	
Recent cardiac pain ½ hr. or longer in duration	25	71.4	4	11.4	6	17	35
Recent cardiac pain less than ½ hr. in duration	19	86.4	1	4.6	2	9	22
No recent cardiac pain	57	53.7	45	42.4	4	3.6	106

0.5 mm. and T-wave inversion of less than 1 mm. is unaccompanied by a reasonable cause for electrocardiographic changes and that such minor ST-T changes are probably within the range of normal. The hyperventilation syndrome or unrecognized physiologic changes must be excluded.

In this series of 106 cases of nonspecific ST and T-wave changes in patients without recent acute cardiac pain there appeared to be a reasonable explanation in 57 patients with such clinical abnormalities as pericarditis, postoperative shock, clinical chronic cor pulmonale, pulmonary embolism, electrolyte disturbances, and chronic angina etc. (table 3). Intracranial disease, which included 10 cases in this series, has been reported as a cause of abnormalities of the ST segment or T wave, or both, when as a direct result of cerebral lesions or mediated through an alteration in serum electrolytes.[4] In almost all of the 49 cases in which there was no apparent clinical cause, the ST-segment and T-wave changes were of minimal degree and may have been insignificant. In the cases of ST-segment and T-wave inversion, which were found in patients with recent acute cardiac pain, the problem was to determine whether the electrocardiographic changes actually developed in connection with the acute pain or were previously present. This could be resolved by a study of previous and subsequent serial electrocardiograms.

Cases with recent cardiac pain could generally be differentiated from those without such pain by an ST-segment depression of more than ½ mm. in the former. In no instance was the ST segment depressed more than 2 mm. in cases without recent cardiac pain, whereas this degree of depression was not uncommon in cases with recent cardiac pain. The difference between cases with and without cardiac pain was more striking if 5 mm. of inversion of the T wave was used as the criterion. In the cases with recent cardiac pain ST-segment depression alone or in combina-

Table 6

Depth of T-Wave Inversion

	5 mm. or greater		2-5 mm.		More than 0.5 mm. up to 2 mm.		0.5 mm. or less		Normal T wave		Total cases in group
	No.	%	No.	%	No.	%	No.	%	No.	%	
Recent cardiac pain ½ hr. or longer in duration	6	17.1	4	11.4	12	34.3	12	34.3	1	2.9	35
Recent cardiac pain less than ½ hr. in duration	6	27.4	5	22.7	7	31.8	3	13.6	1	4.5	22
No recent cardiac pain	4	3.8	8	7.8	43	42.1	47	46	4	3.8	106

tion with T-wave inversion occurred more regularly than in those without recent cardiac pain; in the latter group T-wave inversion was more likely to appear as an isolated finding.

Attention was directed to deep T-wave inversions in the midprecordial leads as described by Pruitt et al.[4] They reported a study of 62 cases with at least 5 mm. of T-wave inversion which was maximal in lead V_3. In 38 of these there was clinical evidence suggesting myocardial infarction or severe ischemia, but in 24 no such clinical evidence was present. Four of the patients in the group with cardiac pain who died and were studied at autopsy showed evidence of subendocardial infarcts. In our series there were 12 cases that showed electrocardiographic changes similar to those in Pruitt's cases. In seven of these there had been recent cardiac pain of ½ hour or longer duration; in two, recent cardiac pain of less than ½ hour duration; and in three, no recent cardiac pain.

An analysis of the ST and T contours disclosed no significant difference between the frequency of an "ischemic" type of ST segment in patients with and without recent cardiac pain. But if the criterion of ¾ mm. or greater depression of the ST segment is added to that of ischemic contour, the combination was found in 78 per cent of the cases of recent cardiac pain and in only 21 per cent of those without such pain. The presence of an "ischemic" contour of T wave appeared to show a good correlation with recent cardiac pain, since such a T wave was observed in 49 per cent of the cases with recent cardiac pain and in only 10 per cent of those without such pain.

To summarize, the probability that the ST-segment depressions and T-wave inversions were associated with and due to the episode of recent acute cardiac pain was indicated by the combination of ST depression ad T-wave inversion with a depth of more than ½ mm. of the ST depression and more than 1 mm. inversion of the T wave, by isolated T-wave inversion of more than 2 mm. and especially by more than 5 mm. in the midprecordial leads, and by an ischemic contour of the ST segment that is depressed more than ½ mm.

The combination of such electrocardiographic findings and a history of recent acute cardiac pain usually indicates that the electrocardiographic changes were caused by recent myocardial ischemia or necrosis. However, it is desirable to confirm such an interpretation by a comparison with previous electrocardiograms if available. Furthermore, serial electrocardiograms showing progressive change or disappearance of the abnormalities usually attest to a relationship to the recent cardiac pain but care should be taken to be sure that there is identical electrode placement and minimal changes should not be emphasized. The effort to differentiate ST-T changes denoting acute myocardial ischemia from acute myocardial necrosis was made by correlating these changes with recent cardiac pain of less than or more than ½ hour duration. It was thought that the pain of briefer duration might represent myocardial ischemia and that of longer duration might indicate myocardial necrosis. But no significant dif-

Table 7

Depth of ST-Segment Depression

	Greater than 2 mm.		More than ½ mm. up to 2 mm.		½ mm. or less		Isoelectric ST segment		Total cases in group
	No.	%	No.	%	No.	%	No.	%	
Recent cardiac pain ½ hr. or longer in duration	6	17.1	16	45.7	11	31.4	2	5.7	35
Recent cardiac pain less than ½ hr. in duration	4	18.2	10	45.4	8	36.4	0	0	22
No recent cardiac pain	0	0	14	13.2	47	44.3	45	42.5	106

Table 8

Contrast of Contour Abnormalities in Cases with and without Recent Cardiac Pain

	Ischemic ST segment and ischemic T wave		Ischemic T wave only		Ischemic ST segment only		Neither ischemic ST segment nor ischemic T wave		Total cases in group
	No.	%	No.	%	No.	%	No.	%	
Recent cardiac pain ½ hr. or longer in duration	14	40	6	17.1	10	28.6	5	14.3	35
Recent cardiac pain less than ½ hr. in duration	6	27.3	2	9.1	7	31.8	7	31.8	22
No recent cardiac pain	8	7.5	3	2.8	29	27.3	66	62.2	106

ferences could be found in the degree of character of ST and T-wave changes in these two groups.

Several considerations may explain the lack of electrocardiographic difference in these two groups of cases classified according to the duration of acute cardiac pain. Many of the patients with recent cardiac pain for more than ½ hour unquestionably experienced extensive myocardial necrosis. But when this was indicated by Q waves as well as ST-T changes they were separated from the group with nonspecific ST-T abnormalities. Evidence has been presented by Cook and others[5] that acute myocardial necrosis is associated with abnormal Q waves as well as ST and T changes when more than 75 per cent of the thickness of the myocardial wall underwent necrosis. When subendocardial necrosis did not exceed 50 to 75 per cent of the thickness of the ventricular wall there was only ST-segment depression and T-wave inversion. Such changes are indistinguishable from subendocardial ischemia in the same area. In fact it is probable that the ST-segment depression and T-wave inversion observed in patients with subendocardial necrosis are due to the associated ischemia rather than to the necrosis itself. Thus, if subendocardial necrosis occurred in the patients with pain lasting more than ½ hour, the electrocardiographic changes would be undistinguishable from those in patients experiencing recent cardiac pain for less than ½ hour even if ischemia and no necrosis was present in the latter group. A differentiation between subendocardial ischemia and subendocardial necrosis would be indicated by differences in the duration and severity of the pain and by various observations and laboratory findings. The electrocardiographic changes themselves could only be reported as indicating subendocardial ischemia or necrosis.

Summary

A study was made of 1,000 consecutive adult in-patient electrocardiograms to deter-

mine the possibility of making a more precise diagnosis than "nonspecific ST and T-wave changes." More than 50 per cent (209) of the 410 abnormal electrocardiograms (exclusive of arrhythmias) were characterized by nonspecific depression of ST segment or T wave inversion, or both.

These 209 cases comprised four groups: (1) 46 patients (22 per cent) had received digitalis, which could account for the ST-T changes; (2) 57 patients (27 per cent) had had an acute episode of cardiac pain within 5 days prior to the electrocardiogram; (3) 57 patients (27 per cent) had had no recent cardiac pain but suffered from some disease that could be regarded as a possible cause for the ST-T changes; and (4) 49 patients (24 per cent) had no apparent cause for the electrocardiographic changes. In the last group, in contrast with the others, the ST-segment depression was less than 0.5 mm. and the T-wave inversion less than 1 mm.

In patients with recent cardiac pain, as contrasted with those without such pain, the electrocardiograms were characterized by a combination of ST depression and T-wave inversion, with a depth of more than ½ mm. of the ST depression and more than 1 mm. inversion of the T wave, by isolated T-wave inversion of more than 2 mm. and especially by more than 5 mm. in the midprecordial leads, and by an ischemic contour of the ST segment that is depressed more than ½ mm.

There was no definite difference in the electrocardiographic findings in the patients with recent cardiac pain of less than ½ hour and those with recent cardiac pain of more than ½ hour when the cases with transmural infarction (Q-wave changes) were excluded. This is compatible with the concept that the electrocardiogram usually does not distinguish between subendocardial ischemia and subendocardial necrosis. The latter differentiation would depend on multiple clinical and laboratory findings.

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The fantastic economies of successful research swiftly go beyond any method of accurate accounting. As an example, I would estimate that the work on the sulfa drugs up to and including the proof of their efficiency in the treatment of lobar pneumonia did not cost more than $150,000. But in as short a time as three years after their value in pneumonia was shown, the saving in life insurance policies that would have been paid by one life insurance company for deaths from lobar pneumonia alone only, on the West Coast of the United States, over one year only, was calculated at $3,000,000. In such ways research gives a continuing and a permanent lift to Great Medicine.—ALAN GREGG, M.D., *Challenges to Contemporary Medicine.* New York, Columbia University Press, 1956, p. 71.

Aortic Valve Perforation in Bacterial Endocarditis

By RALPH TOMPSETT, M.D., AND GLENN D. LUBASH, M.D.

THE MODERN TREATMENT of bacterial endocarditis may be expected to result in bacteriologic cure in 90 to 95 per cent of patients who complete a course of treatment. Nevertheless as many as 25 per cent of patients die from emboli or cardiac failure within the first 6 months from initiation of treatment.[1, 2] In addition to the underlying heart disease, the additional factor of destruction of all or part of a valve may be added during the course of bacterial endocarditis and contribute to congestive heart failure, despite bacteriologic cure. The importance of the development of dynamically significant aortic insufficiency during the course of bacterial endocarditis has been described in numerous case reports and various authors have commented on its significance.[3-8]

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During the course of observation of approximately 150 patients with proved bacteriologic endocarditis over a 10-year period we have also recognized the importance of this complication appearing during treatment or the early convalescent period. Moreover, the clinical features have seemed to be reasonably typical in most cases and, when present, have generally been followed by progressive, often intractable heart failure. The recent interest in surgical procedures that may afford a significant chance of improvement in these patients has made it seem worthwhile to review the problem with a view to directing attention

Table 1

Summary Data on Patients with Aortic Valve Perforation in Bacterial Endocarditis

Case no.	Sex	Age	Type of heart disease	Cusp involved	Lesion of cusp	Relation of signs of aortic insufficiency to endocarditis	Duration of life after either appearance of or change in signs of aortic insufficiency (mo.)
1	M	49	Syphilitic	Posterior and right	Perforation	Changed	3-5
2	M	47	Rheumatic	Posterior and left	Perforation	Appeared	1
3	M	48	Congenital (IV septal defect)	Posterior, right and left	Perforation and rupture	Appeared	33
4	M	43	Rheumatic	Right and left	Perforation	Uncertain, probably new	2-6
5	M	55	Uncertain, probably rheumatic	Posterior	Perforation	Appeared	3
6	F	53	Rheumatic	Posterior and left	Perforation	Appeared	½ to 6
7	F	55	Rheumatic	Right	Perforation	Changed	3
8	F	64	Rheumatic	Right	Perforation and rupture	Appeared	8
9	M	30	Rheumatic	Posterior	Perforation	Changed	4
10	M	71	Rheumatic	Posterior	Perforation	Appeared	2-8

to the recognition of this complication of bacterial endocarditis.

The present report summarizes observations in patients with bacterial endocarditis seen at the New York Hospital between 1944 and 1956, in whom dynamically significant aortic insufficiency appeared after initiation of therapy and in whom postmortem examination revealed perforation or destruction of one or more aortic valve cusps.

Observations

The postmortem records at the New York Hospital from January 1944 to January 1956 were reviewed. Forty-seven cases of bacterial endocarditis were autopsied during this period. The clinical records were reviewed and compared with the postmortem observations. Those cases were chosen that fulfilled the following criteria:

1. Absence of dynamically significant aortic insufficiency prior to the development of endocarditis. 2. The development of dynamically significant aortic insufficiency during or soon after treatment. 3. Autopsy evidence of either perforation or destruction of an aortic valve cusp due to bacterial endocarditis.

Ten suitable cases were found and are summarized in table 1. A representative illustration of the changes seen in the aortic valve is presented in figure 1.

Discussion

These cases illustrate what appears to be an important complication of bacterial endocarditis, namely, perforation or destruction of the aortic valve cusps. In all of the patients, bacteriologic cure of the endocarditis had been achieved or could reasonably have been anticipated had it not been for the fact that progressive cardiac failure supervened.

It is impossible to estimate the frequency of aortic valve perforation in bacterial endocarditis from the data at hand. During the 12 years covered by this study, approximately 150 patients at this hospital were recognized during life to have bacterial endocarditis and treated for it. Forty-seven cases were autopsied during this period. (It should be noted that not all of these were recognized during life and treated.) Of those cases autopsied, 15 had perforation of the aortic valve. Although only 10 cases are included here because of the criteria mentioned in the introduction, it is possible that aortic valve perforation was an important factor in other patients as well.

Figure 1

The aortic valve in case 9. The posterior cusp exhibits a large perforation, 1.5 cm. in diameter.

The very complexity of the clinical situation in which valve perforation occurs tends to obscure the fact that valve perforation has occurred and that the likelihood of progression to intractable heart failure is good. It is hoped that a greater awareness of the importance of aortic valve perforation in bacterial endocarditis coupled with improved surgical procedures for correction of aortic insufficiency may enhance the outlook for this group of patients.

Summary

This report describes 10 patients with bacterial endocarditis who during observation developed signs of dynamic aortic insufficiency or experienced marked worsening of the manifestations of pre-existing aortic insufficiency. The autopsy findings in these patients provide evidence that the clinical signs were associated with perforation or rupture of the aortic valve cusps. It is suggested that this sequence of events in the course of bacterial endocarditis is common and that its occurrence must be regarded as an ominous prognostic sign.

Acknowledgment

The authors are grateful to Dr. John Kidd of the Department of Pathology, Cornell University Medical College, for permission to review the autopsy records on the cases reported herein.

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To put the discovery of the systemic circulation of the blood in its true light, we must have some notion of the history of philosophy, science and medicine. Medicine, and herein it is in contrast with Theology and Law, had its sources almost wholly in the Greeks. Not only in the doctrine of the four elements of Empedocles, a doctrine which has survived almost to our own day, and in the physical theories of Heraclitus and Leucippus, did medicine, for good or ill, first find a scheme of thought, but in the schools of Hippocrates and of Alexandria it was based also, and far more soundly, upon natural history and anatomy. The noble figure of Galen, the first experimental physiologist and the last of the great Greek physicians, stood eminent upon the brow of the abyss when, as if by some convulsion of nature, medicine was overwhelmed for fifteen centuries. To the philosophy of medicine, Galen had given more than enough; to its natural history he had contributed in the following of Hippocrates; to its discoveries he had given the greatest of all means of research, individual genius; to its methods he had given, but in vain, that indispensable method, practised first perhaps in history by Archimedes and the Alexandrians, of verification by experiment; a method, after Galen, virtually lost till the time of Gilbert, of Galileo and of Harvey.—THOMAS CLIFFORD ALLBUTT, M.A., M.D. *Science and Medieval Thought*. London, C. J. Clay and Sons, 1901, p. 20.

Atrial Septal Defect in the Aged

By MANUEL RODSTEIN, M.D., FREDERIC D. ZEMAN, M.D., AND ISADORE E. GERBER, M.D.

THE less obvious diseases occurring in the aged are often overlooked in clinical practice and have been given little mention in medical literature. Atrial septal defect has a high incidence in youth and middle age. Among individuals over the age of 50 it is the most common major congenital defect.[1] The refinement of diagnostic criteria is made imperative by the fact that rapidly progressive cardiac failure (of relatively recent origin) may occur in cases with atrial septal defect over the age of 60. Ellis has shown that such individuals may be successfully operated upon, with closure of the defects, and symptomatic improvement.[2] In the aged a well-defined clinical picture is often present, and may be seen with minimal impairment of cardiac function and no significant cardiac symptoms.

In view of these considerations we are presenting the clinical and pathologic findings in two cases over the age of 70. One of these survived to the age of 84 years, and is the oldest case of atrial septal defect yet reported. We have combined the findings in these two cases with those in 16 other cases (65 years of age or older) reported by other authors with postmortem findings[3-16] in order to determine common clinical features and explain the reasons for prolonged survival.

Case Reports

Case 1

An 84-year-old man had a history of dyspnea for 8 years, congestive heart failure for 2 years, and repeated attacks of bronchopneumonia and anginal pain. His blood pressure was 215/90; basal systolic and diastolic murmurs were present, no cyanosis was found. Enlargement of the right ventricle, of the right atrium, and of the pulmonary artery was present on x-ray (fig. 1), and a hilar dance was noted on fluoroscopy (figs. 2 and 3). Regular sinus rhythm with right bundle-branch block was present in his electrocardiogram. The clinical diagnosis of atrial septal defect was made. After 7 years of observation death resulted from congestive heart failure. At postmortem examination a high atrial septal defect 2 cm. in diameter was found in a 520-Gm. heart with hypertrophy of the right ventricle and atrium, and dilatation and severe atheromatosis of the pulmonary artery (fig. 4).

Case 2

A 72-year-old woman gave a history of dyspnea for over 18 years, congestive heart failure for over 9 years, recurrent attacks of bronchopneumonia, and persistent cyanosis. Her blood pressure was 205/95. A basal systolic murmur was constantly observed. An enlarged right atrium, right ventricle, and pulmonary artery were present on x-ray; hilar dance was not noted. Atrial flutter and right bundle-branch block were noted electrocardiographically. The clinical diagnosis of atrial septal defect was made. Death was due to congestive heart failure and bronchopneumonia. At postmortem examination a 2.5 by 3 cm. foramen ovale was found with the pulmonary vein from the right upper lobe emptying into the right atrium (fig. 5). The right atrium and ventricle were hypertrophied; the pulmonary artery was dilated.

Discussion

We have collected from the literature 16 cases of atrial septal defect coming to postmortem examination over the age of 65 years[3-16] and combined their data with our two cases (tables 1 and 2). We have omitted published cases in which clinical and postmortem data were not adequate. We have not included cases in which another congenital cardiac defect predominated, such as that of Adams and Hudson.[17] In this case a 79-year-old woman, who died of cholangiohepatitis without any antecedent signs or symptoms of cardiac disease, was found to have a predominant Ebstein's anomaly with an atrial septal defect 1.7 cm. in diameter of the ostium secundum type.

The age of the group ranged from 67 to 84 years for the men and from 70 to 82 for the women, with an average age of 75 years.

From the Medical Services, The Home for Aged and Infirm Hebrews of New York, New York.

Table 1

Clinical Characteristics

Author		Age	Sex	Duration of congestive heart failure	History of broncho pneumonia	Angina	Duration of dyspnea	B.P.	Cyanosis	Basal diastolic murmur
Rodstein, M. et al.	1)	84	M	2 yr.	+	+	8 yr.	215/90	0	+
(Reported in this paper	2)	72	F	Over 9 yr.	+	0	Over 18 yr.	205/95	+	0
Ellis, F. R., et al.[3]		82	F	Terminal	0	0	8 yr.	145/100	0	+
Rosenthal, L.[4]		81	F	4 yr.	0	+	6 yr.	180/120	0	0
Stannus, D. G. et al.[5]		70	M	14 yr.	0	0	14 yr.	122/65	0	+
Tarnower, H. et al.[6]		77	F	2 wk.	0	+	6 wk.	170/110	0	0
Colmers, R. A.[7]	1)	68	M	one episode	0	+	—	—	0	+
	2)	78	M	8 yr	0	0	8 yr.	150/90	0	+
	3)	72	M	8 yr	0	0	50 yr. Asthmatic	110/68	0	0
Askey, J. M. et al.[8]		72	M	3 yr.	+	0	15 yr.	—	slight	0
Pepper, D. S. et al.[9]		77	F	0	+	0	6 mo.	—	—	0
Sailer, S.[10]		67	M	5 mo.	0	0	Over 5 yr.	104/80	0	+
Tinney, W. S., Jr.[11]		76	M	Terminal	0	0	3 wk.	144/64	0	0
Erickson, C. W. et al.[12]		68	M	14 yr.	0	0	14 yr.	155/90	+	0
Espino-Vela, J.[13]		71	F	Marked, duration not noted	—	0	Marked, duration not noted	—	Very slight	0
Case Records #40341[14] Mass. General Hospital		74	M	0	0	0	2 yr.	140/90	None	0
Case Records #42092[15] Mass. General Hospital		83	F	0	0	0	1 yr.	110/60	None	0
Case Records #44411[16] Mass. General Hospital		70	F	Several years	0	0	0	180/80	0	0

Eight were female and 10 were male. This incidence is at variance with the female preponderance found in younger groups: Campbell and associates[18] found a 7 to 1 ratio in those over 20 years of age. This phenomenon, which is even more striking in view of the general female preponderance at advanced ages, may perhaps be explained in the same way Wood[19] explained the predominance of women in cases of atrial septal defect with pulmonary hypertension. He considered it related to the occurrence of pulmonary emboli during pregnancy. Since pulmonary hypertension has an adverse effect on prognosis, more men might be expected to survive to advanced ages. Of the five cases between 60 and 64 operated on by Ellis, however, four were female.[2]

The history of repeated attacks of bronchopneumonia in four of the group has been noted as common in atrial septal defect and attributed to the susceptibility of the hyperemic lung to minor upper respiratory infections.[1, 20] Successful treatment of bronchopneumonia with antibiotics may in part be responsible for the prolonged survival of some of our cases, particularly case 1, in which at least five attacks were observed in 7 years.

The occurrence of angina in four of the group, a symptom not reported in young and middle-aged persons with atrial septal defects, may be attributed to coronary artery sclerosis in the presence of marked right ventricular hypertrophy.

The occurrence of dyspnea of many years' duration before the onset of overt congestive heart failure in 10 of the group has been noted as a common finding in atrial septal defect at all ages, and is attributed to the reduced air space in the lungs due to the excessive occupation of space by hyperemic blood vessels secondary to greatly increased pulmonary blood flow.[21]

Cyanosis of appreciable duration and intensity was noted in only two cases. We have not considered significant the description of slight cyanosis in pre-terminal cases with associated mitral stenosis and in severe congestive heart failure as described in the aged cases of Askey and Kahler[8] and Espino Vela.[13] Slight cyanosis is frequently seen in cases of uncomplicated mitral stenosis in failure and is attributable to peripheral circulatory stasis. The rarity of cyanosis is surprising, since Campbell's group[18] found a considerable incidence of central cyanosis in their cases in the fourth and fifth decades of life. It may be attributed to pulmonary hypertension not sufficient to cause a reversal of the principal atrial shunt to a right-to-left direction. Ellis and associates[2] noted no case over 60 years of age with a predominant right-to-left shunt.

In the case of Erickson and Willius,[12] cyanosis may be attributed to the huge size of the atrial septal defect, with a consequent pooling of atrial blood and marked bidirectional shunting.[22] Persistent cyanosis in our case 2 may have been due to long-standing heart failure and to anomalous pulmonary venous drainage into the right atrium. Campbell and co-

Figure 1

Case 1. Chest film of 84-year-old man, July 7, 1952, 6 years before death, showing marked enlargement of the pulmonary artery and its main branches and absence of the aortic knob.

Table 2

Laboratory and Postmortem Findings

Author	Laboratory findings: ECG	Rhythm	Fluroscopy	Chest x-ray	Postmortem findings: Cause of death	Heart weight, Gm.	Description of defect	Mitral stenosis
Rodstein, M. et al. (Reported in this paper)	1) Rt. BBB	RSR	Hiler dance	Same	CHF	520	2 cm. diam. high	0
	2) Rt. BBB	Atrial flutter	——	Same	CHF Broncho-pneumonia	—	2.5 × 3 cm. foramen ovale A pulmonary vein emptied into the right atrium	0
Ellis, F. R. et al.[3]	Rt. BBB	Atrial flutter 3 yr.	Hilar dance	Typical RV, RA, PA	Penetrating ulcer, CHF	525	2.5 × 3.5 anterior and above foramen ovale	+?
Rosenthal, L.[4]	——	Irregular terminal	——	Same	CHF	—	2 cm. diam.	+
Stannus, D. G. et al.[5]	Rt. BBB	Atrial fibr. 14 yr.	——	Same	Broncho-pneumonia	—	3.3 × 2.8 cm.	+
Tarnower, H. et al.[6]	RAD	Atrial fibr.	——	Same	CHF	—	4 cm. foramen ovale	0
Colmers, R. A.[7]	1) Rt. BBB	——	——	Same	Coronary thrombosis	635	2.5 diam. ostium secundum	0
	2) Inc. Rt. BBB	Atrial fibr.	——	Same	CHF	850	3 × 4 ostium secundum	0
	3) Inc. Rt. BBB	Atrial fibr.	——	Same	CHF	634	4.5 × 2.5 ostium secundum	0
Askey, J. M. et al.[8]	Inc. Rt. BBB	Atrial fibr.	——	Same	CHF and Uremia	840	Large-lower edge over mitral & tricuspid valves	+
Pepper, D. S. et al.[9]	——	——	——	——	Sulfa block kidney	280	0.8 cm. diam.	0
Sailer, S.[10]	Right preponderance	RSR	——	——	Pneumonia	700	3 cm. diam.—lower edge over tricuspid valve-foramen ovale closed	+
Tinney, W. S. Jr.[11]	Slurred & low QRS	A-V nodal rhythm	——	——	CHF	860	4.5 cm. foramen ovale	0
Erickson, C. W. et al.[12]	Right ventricular preponderance, T_2, T_3 inverted	Atrial fibr. 2½ years, complete heart block	——	Same	Acute myocardial infarction	880	10 × 7 cm. foramen ovale	0
Espino-Vela, J.[13]	RV hypertrophy	Atrial fibr.	Hilar dance	Typical RA, PA	RV, CHF	—	3.5 cm. diam. foramen ovale	+
Case Records #40341[14] Mass. General Hosp.	Normal (No BBB)	RSR	——	——	Paradoxical emboli	250 (normal findings	"large patent foramen ovale"	0
Case Records #42092[15] Mass. General Hosp.	Normal (No BBB)	Atrial fibr.	——	Normal	Pulmonary emboli Paradoxical emboli	— (normal findings)	0.5 cm. foramen ovale	0
Case Records #44411[16] Mass. General Hosp.	Normal leads	RSR	——	——	Multiple paradoxical emboli	—	2 cm. foramen ovale	0

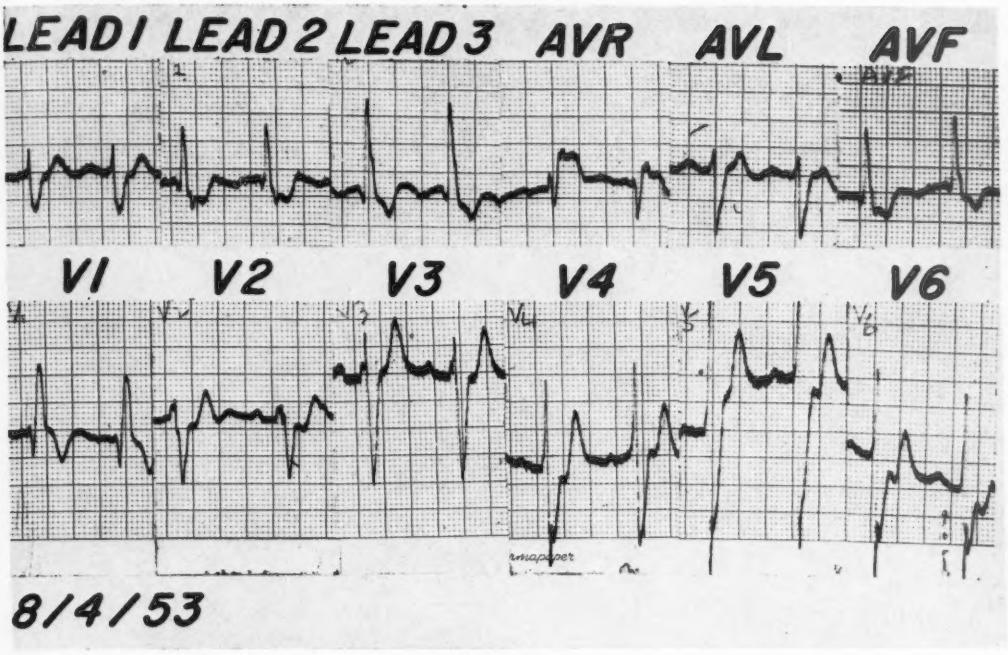

Figure 2

Case 1. Electrocardiogram of 84-year-old man, August 4, 1953, 5 years before death, showing right bundle-branch block and regular sinus rhythm.

workers[18] thought that this causes an additional large fixed left-to-right shunt that cannot become smaller with exercise. Wood[23] included hemi-anomalous pulmonary venous drainage into the right side of the heart among the causes of severe pulmonary hypertension and cyanosis. On the other hand, Guntheroth et al.[24] did not find cyanosis in 10 such cases studied with cardiac catheterization ranging in age from 2 to 40 years. Levinson et al.[25] demonstrated only slight pulmonary hypertension on catheterization of such cases.

The absence of significant pulmonary hypertension in many elderly patients with atrial septal defect must be regarded as an important factor in their survival. The factors that cause pulmonary hypertension are repeated respiratory infections, pulmonary thrombosis and pulmonary embolism, particularly associated with pregnancy, and a failure of the pulmonary vascular resistance to fall low enough after birth to prevent slight pulmonary hypertension from increased flow.[19] Kelly and Lyons[20] have reported pulmonary hypertension in only seven of 19 patients over the age of 45 years; and in two over the age of 70 it was absent on cardiac catheterization. Coulshed and Littler[26] found a pulmonary artery pressure of 50/20 in a patient aged 68. Ellis et al.[2] reported that 20 of 38 cases 40 years of age and over had systolic pulmonary artery pressures less than 60 mm. of mercury. Patients with atrial septal defect who develop high pulmonary pressures die at an average of 36 years of age.[27] Those who do not, develop considerable intolerance to effort as a rule between 50 and 60 years of age; if they remain in regular sinus rhythm effort, intolerance may not be manifest until after the age of 60.

Atrial septal defect is the only congenital cardiac defect with a significant incidence of atrial fibrillation. Campbell et al.[18] noted that

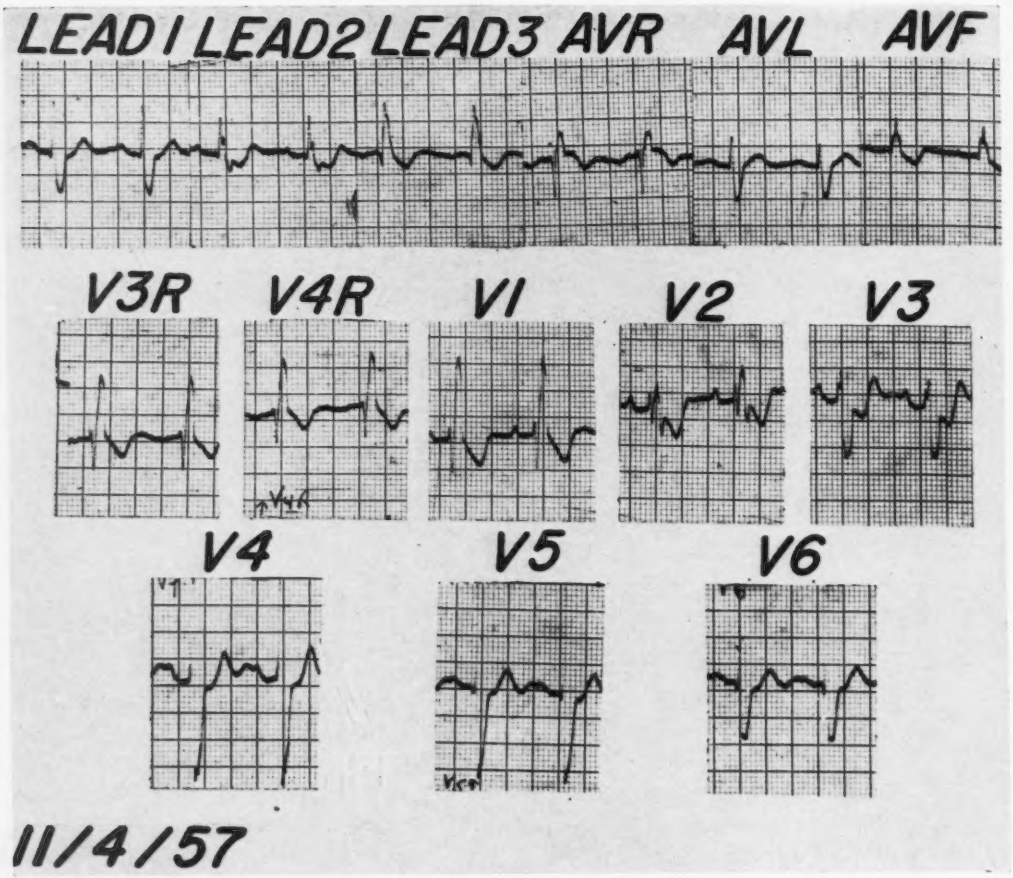

Figure 3

Case 1. Electrocardiogram of 84-year-old man, November 4, 1957, 4 months before death, showing persistent right bundle-branch block, regular sinus rhythm, and evidence of right ventricular hypertrophy.

death usually occurs within 5 to 10 years of its onset, after a period of reduced function. Wood[27] found it occurring as early as 17 years of age in cases of atrial septal defects and accompanied by effort intolerance. He thought that the cause of failure was nearly always the onset of atrial fibrillation, which in previously uncomplicated cases occurs at an average age of 50. The atrial fibrillation results immediately in tricuspid incompetence (a matter of a few seconds). The tricuspid incompetence elevates the right atrial pressure during systole and makes the interatrial shunt diastolic rather than systolic, but does not alter materially the magnitude of the left-to-right shunt. The limited left ventricular filling and systemic output is further diminished by lack of atrial support, a constant effect of atrial fibrillation in any condition. The flow ratios remain much the same because the right ventricular output also falls from a combination of the atrial fibrillation and the tricuspid incompetence. The breakdown, which manifests itself in fatigue, high venous pressure, hepatic enlargement, and edema, is due to a combination of a low cardiac output with impaired renal flow and right ventricular failure with tricuspid incompetence. This

breakdown is very sudden but under medical treatment patients may expect another 10 years or more of life, and do not suffer unduly until toward the end; indeed, some of them remain remarkably well and continue thier occupations despite their handicap.

So long as a patient with atrial septal defect remains in normal rhythm and is uncomplicated by pulmonary hypertension, which most are, they may continue almost symptom free to well over 60, or even into old age.

In this group electrocardiographic records were described in fourteen cases. Atrial fibrillation was present in eight, atrial flutter in two, atrioventricular nodal rhythm in one, and regular sinus rhythm in only three cases. The duration of the arrhythmias was noted in only three of the cases, 2½, 3, and 14 years. We assume that in the light of the above observations by Wood,[27] atrial fibrillation probably developed late in life in these aged individuals.

Four of five of Ellis's cases who developed rapidly progressive congestive heart failure between 60 and 64 years of age had atrial fibrillation.[2]

Blood pressure determinations were available in 14 of the 18 cases. The pulse pressure exceeded 40 in all but two, and in eight systolic and diastolic hypertension was present. In younger cases a pulse pressure over 40 is rare and the systolic pressure rarely exceeds 120. Even lower levels are found in children.[18] These differences may be accounted for by the increased incidence of hypertension in the aged and changes in aortic elasticity with aging could yield the widened pulse pressures.

Right bundle-branch block, complete or incomplete, is common in atrial septal defect and was present in almost all of these aged cases with defects of significant size, i.e., over 1 cm. in diameter. This has been attributed to diastolic overload of the right ventricle or to hypertrophy of the crista supraventricularis.

In all cases the chest roentgenograms showed typical findings when the defect exceeded 1 cm. in diameter. Cardiac fluoroscopy revealed a characteristic hilar dance in each of the three cases reported as being fluoroscoped (expansile pulsation of the pulmonary arteries spreading to their smaller branches).

Figure 4

Case 1. Right side of heart of 84-year-old man, showing the arrow pointing to a 2 cm. atrial septal defect in the extreme superior portion of the interatrial septum. The probe in the fossa ovalis demonstrates a patent foramen ovale.

In six cases without mitral stenosis and with defects of significant size, the average heart weight was 730 Gm. This far exceeds the average weight of 469 Gm. reported by Roesler[28] for such cases over the age of 14 years.

In three cases complicated by mitral stenosis an average heart weight of 688 Gm. was found. Schnitker[29] found the reverse, i.e., a greater average heart weight in cases with associated mitral stenosis.

At postmortem examination the findings of right ventricular hypertrophy, right atrial and pulmonary artery dilatation, and small left ventricle and aorta were similar to those found in younger cases.

The location and type of septal defect was given in 15 of the cases. Two were of the rare ostium primum type. Eleven were of the secundum type located in the area of the fossa ovalis, and two were high atrial septal defects. The two high defects were our patient 1 who survived to 84 years, and Ellis's[3] patient, who reached 82 years, the two oldest cases in the literature. The defects were 2 and 2.5 cm. in diameter, respectively, which

Figure 5

Case 2. Right side of the heart of a 72-year-old woman, showing a 3 × 2.5 cm. atrial septal defect of the secundum type at the site of the foramen ovale (arrow A) and the pulmonary vein from the upper lobe of the right lung entering into the right atrium immediately adjacent to the entrance of the superior vena cava (arrow B.)

are smaller than those usually found in younger patients. The secundum lesions ranged up to 4.5 cm. in diameter. Watkins and Gross[30] have noted this difference in size between high and mid-atrial defects. Ellis et al.[2] noted that the defects in their operated cases over 60 years were smaller than those usually found in younger patients. Associated anomalous pulmonary vein drainage reported as common in high defects by Lewis[31] were not noted.

Burnett and White,[21] however, thought that in their series the size of the defect did not affect the length of life, provided it exceeded 1 cm. in diameter.

Defects less than 1 cm. in diameter are of no clinical significance except for the occurrence of paradoxical pulmonary emboli. In the usual etiology of this condition a large pulmonary infarct causes a rise in pulmonary resistance sufficient to cause reversal of flow through a patent foramen ovale or other septal defect, to a right-to-left direction. A subsequent embolus, usually from a thrombosed leg vein, may then pass through the defect into the arterial circulation. Such supposedly rare paradoxical emboli were present in three of this aged group. The foramina ovale were described as 2 cm., 0.5 cm., and large in diameter. The great majority of cases of paradoxical embolization probably have only probe-patent (0.2 cm.) or pencil-patent (0.7 cm.) foramina ovale preceding the first pulmonary embolization, and these become functionally patent only after the right atrial pressure rises subsequent to the embolization. Two of the three cases with paradoxical emboli in this group had no cardiac hypertrophy or other significant abnormalities indicative of a preceding significant atrial septal defect. In a review series of 101 cases of paradoxical emboli, Gill and Dammin[32] found 27 over the age of 60.

The leading cause of death was the same as that found in atrial septal defect at all ages, congestive heart failure.

The coexistence of mitral stenosis in six of the group is high, considering the present opinion of the rarity of the so-called Lutembacher syndrome.[13, 20, 33] Kelly and Lyons[20] thought that the high incidence in the early literature probably resulted from misinterpreting the fibrous and calcific beading of the mitral leaflets as mitral stenosis. Such changes are common in elderly subjects. McGinn and White[34] noted that the average life span was less than that of either uncomplicated atrial septal defect or mitral stenosis. White[35] thought that the mitral stenosis is of no aid to a person with atrial septal defect in dealing with the burden on his right heart and pulmonary artery. In severe mitral stenosis an atrial septal defect may be helpful only by preventing acute pulmonary edema with a

tachycardia. Most authors[13, 29] consider the relationship coincidental with mitral stenosis resulting from rheumatic fever.

Summary and Conclusions

The clinical and pathologic findings in two cases of atrial septal defect, a male aged 84 years and a woman aged 72 years, are presented. The findings in these cases are combined with those in 16 other cases of atrial septal defect confirmed at postmortem examination, over the age of 65 years, found in the literature.

The clinical picture of atrial septal defect in the aged is sufficiently similar to that found in younger individuals to permit of a high degree of clinical accuracy of diagnosis.

The differences found between the clinical and pathologic findings in the aged and those found in younger individuals were (1) higher incidence of angina in the aged, (2) higher pulse and blood pressures in the aged, (3) an increased incidence of atrial fibrillation and flutter in the aged, (4) less frequent cyanosis in the aged, (5) a higher incidence of males in the aged, (6) heart weight much increased in the aged, and (7) a lower incidence of pulmonary hypertension in the aged.

The two oldest cases both had defects high in the atrial septum above the fossa ovalis.

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What we know and what we think is not a new fountain gushing fresh from the barren rock of the unknown at the stroke of the rod of our own intellect, it is a stream which flows by us and through us, fed by the far-off rivulets of long ago. As what we think and say to-day will mingle with and shape the thoughts of men in the years to come, so in the opinions and views which we are proud to hold to-day, we may, by looking back, trace the influence of the thoughts of those who have gone before. Tracking out how new thoughts are linked to old ones, seeing how an error cast into the stream of knowledge leaves a streak lasting through many changes of the ways of man, noting the struggles through which a truth now rising to the surface, now seemingly lost in the depths, eventually swims triumphant on the flood we may perhaps the better learn to appraise our present knowledge, and the more rightly judge which of the thoughts of to-day is on the direct line of progress, carrying the truth of yesterday on to that of to-morrow, and which is a mere fragment of the hour, floating conspicuous on the surface now but destined soon to sink, and later to be wholly forgot.—Sir M. Foster. *Lectures on the History of Physiology.* London, Cambridge University Press, 1901, p. 1.

Relationship between Arterial Pressure and Negative U Waves in Electrocardiograms

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ALTHOUGH HYPERTENSION is a common pathologic condition associated with negative U waves in the electrocardiogram, their clinical significance and relationship to arterial pressure have not been adequately established.

Kemp et al.[1] have described a correlation between negative U waves in left precordial leads and malignant hypertension with congestive heart failure. Reversal of the waves from negative to positive or isoelectric has been noted after sympathectomy[2] and, as reported by Surawicz, Kemp, and Bellet,[3] following the lowering of arterial pressure presumably with one of the antihypertensive agents, administration of nitroglycerin, and incidental slowing of the heart rate.

These observations suggest that inverted U waves in electrocardiograms of hypertensive patients might bear some relationship to the arterial pressure but do not make clear whether the level of the arterial pressure is the critical factor in determining their polarity.

The present study was undertaken to determine the possible relationship between arterial pressure and degree of negativity of U waves in electrocardiograms of hypertensive patients and to evaluate their clinical significance.

Methods and Material

The active files of the Research Division of the Cleveland Clinic were reviewed. Records of hypertensive patients who have had negative U waves in one or more of the left precordial leads of the electrocardiogram and who, following antihypertensive treatment, had repeat electrocardiographic tracings constitute material for this study. A total of 45 records was selected. Funduscopic examinations performed during each visit and arterial pressure measurements at least four times daily in supine and standing positions were available in all. Since arterial pressure measurements were not performed simultaneously each electrocardiographic tracing, for purposes of comparison, the average supine arterial pressure of that day was used.

In addition, in 12 hypertensive patients, who on their recent admission to the Research Ward of the Cleveland Clinic Hospital had negative U waves in one or more of the left precordial leads, the arterial pressure was lowered with intravenous sodium nitroprusside as previously described,[4] and simultaneous electrocardiograms were taken serially. In each patient the arterial pressure, measured sphygmomanometrically every half minute, was kept, with the use of sodium nitroprusside, at various desired levels for as long as it was necessary to obtain electrocardiographic tracings. Only the leads showing the negative U waves were taken. In three of these 12 patients, electrocardiograms were also taken during and after intravenous infusion of guanethidine, in both supine and head-up tilt positions.

Results

Review of the Records of 45 Hypertensive Patients with Negative U Waves

Negative U waves in one or more of the left precordial leads of the electrocardiogram were present in all. In nine, negative U waves constituted the only electrocardiographic abnormality. Severe hypertensive retinopathy with exudates, hemorrhages, and papilledema were present in 15, history or physical findings of cerebrovascular complications in nine, angina pectoris in five, and old myocardial infarction in two. Twenty had essential hypertension; 15, the malignant syndrome; and in 10 the hypertension was associated with renal arterial lesions, as demonstrated by renal arteriography. During the follow-up period, which ranged from 4 months to 7 years subsequent to the initial electrocardiogram showing a negative U wave, seven of the 45 patients died. The

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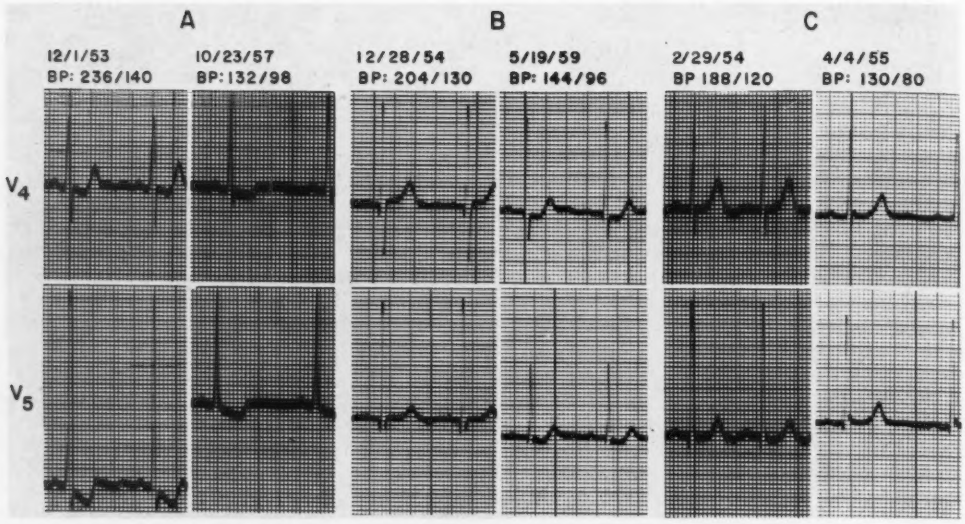

Figure 1

Leads V_4 and V_5 of three hypertensive patients before and after control of elevated arterial pressure. The U waves became upright after treatment and the voltage of R waves decreased.

cause of death was severe nephrosclerosis in three, cerebrovascular thrombosis in one, acute myocardial infarction in one, and unknown in the remaining two.

Following institution of antihypertensive treatment and lowering of arterial pressure, previously inverted U waves became upright (fig. 1) or isoelectric in 31 of the 45 patients, less inverted or diphasic in five, and remained unchanged in four. In the remaining five, average arterial pressure fall was insignificant; the negative U waves remained unchanged in all. A direct correlation between arterial pressure levels and negativity of U waves existed in 41 patients and this correlation persisted during the long period of study. In nine of them, elevation of arterial pressure on a few occasions during the follow-up period resulted in re-inversion of the U waves which, with further treatment and control of arterial pressure, disappeared again.

Average supine arterial pressure in the 31 patients in whom conversion of negative U waves took place was 208/126 before antihypertensive treatment and 159/97 after treatment. All four patients in whom conversion of negative U waves did not take place despite a satisfactory fall of arterial pressure, had a history of stroke, with angina pectoris (in two) and old myocardial infarction (in one). The nine patients with isolated negative U waves had no history or clinical evidence of coronary or cerebral arterial disease; lowering of arterial pressure resulted in conversion of the negative U waves in all. In the seven patients who died, the last available electrocardiogram taken 4 days to 6 months prior to death showed upright U waves and the arterial pressure was well controlled in all.

Effect of Intravenous Sodium Nitroprusside and Guanethidine

In all 12 patients, lowering of arterial pressure with intravenous sodium nitroprusside (100 to 400 μg. per minute) resulted in conversion of negative U waves to positive ones, which lasted as long as the arterial pressure was maintained at normal levels. When the sodium nitroprusside was discontinued, arterial pressure rose to the preinjection levels and the U waves became negative again (fig. 2).

Study of degree of negativity of U waves

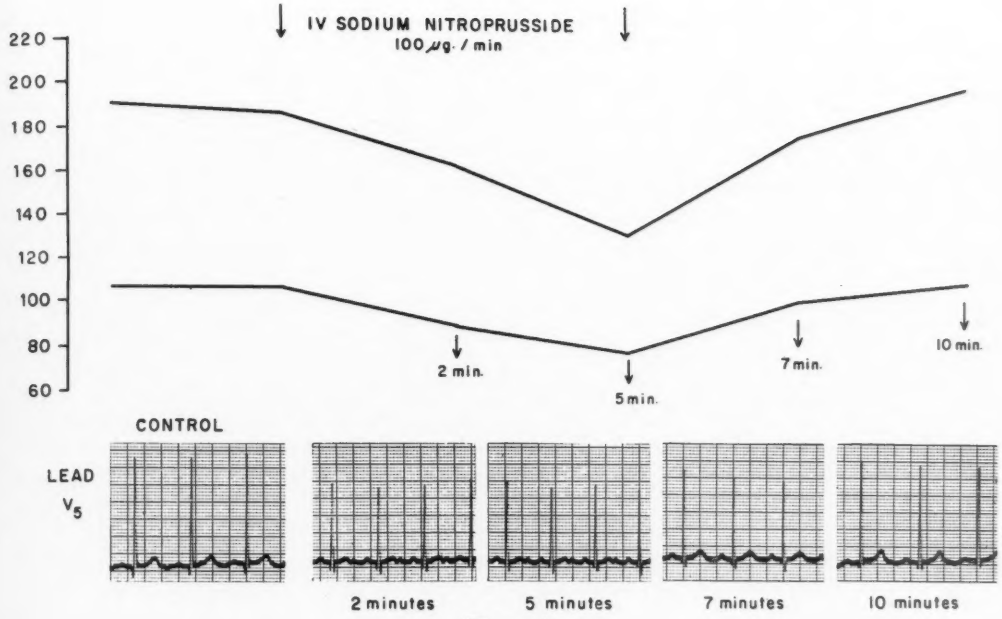

Figure 2

Effect of lowering of arterial pressure by intravenous sodium nitroprusside in a 60-year-old hypertensive man. The negative U waves became upright with lowering of arterial pressure and the voltage of R waves decreased. After discontinuation of the drug, the arterial pressure and electrocardiogram returned to control conditions.

at various levels of arterial pressure showed a gradual decrease in negativity proportional to arterial pressure fall. For each patient there was an arterial pressure level below which U waves became upright or isoelectric. In all, the polarity of U waves was related directly to the arterial pressure and was not primarily influenced by changes of the heart rate.

In one patient with atrial premature beats during a control period with direct arterial pressure recording, it was noted that negative U waves became upright with premature contractions during which the arterial pressure fell to normal. The beat following the premature contraction showed higher direct arterial pressure and more sharply inverted U wave than during periods when the rhythm was regular (fig. 3).

In the three patients in whom intravenous guanethidine was given, the initial pressor effect produced by this drug was associated with an increase of the negativity of U waves, whereas during the following period of the depressor effect, the U waves became upright. Tilting of the three patients prior to intravenous infusion of guanethidine did not result in change of the arterial pressure or the polarity of U waves. Tilting of the same patients after the infusion of intravenous guanethidine resulted in lowering of the arterial pressure and upright conversion of the U waves.

Changes in the polarity of the negative U waves were associated in six of the 12 patients with T-wave changes (diphasic T waves and of less amplitude than before). In eight patients lowering of the arterial pressure also resulted in a decrease of the amplitude of the R waves in the left precordial leads (fig. 2).

Discussion

The results indicate a direct correlation between arterial pressure levels and negativity

Figure 3

Direct brachial arterial pressure recorded with strain-gage manometer and lead V_5 in a hypertensive patient having atrial premature contractions. The U waves vary in relation to arterial pressure.

of U waves in electrocardiograms of hypertensive patients, regardless of the severity and type of hypertension. This correlation was not only observed during periods ranging from 4 months to 7 years, but also in acute experiments in which it was shown that there is a level of arterial pressure below which a negative U wave becomes upright.

Since negativity of U waves in hypertensive patients increases with increase in arterial pressure and remains unchanged with unsatisfactory control of hypertension, the prognostic significance of persistent negative U waves in the electrocardiograms might reflect inadequate antihypertensive treatment without necessarily representing an additional grave prognostic sign. Change in the polarity of negative U waves following control of hypertension may indicate that these waves are not manifestations of organic changes in the myocardium, as suggested by Palmer,[5] but rather are related to high arterial pressure levels.

Lepeschkin[6] has observed that in many pa-

tients with angina pectoris the U waves become inverted during the second through the fourth minute after exercise. We have observed this in one hypertensive patient with coronary arterial disease in whom simultaneous arterial pressure measurements were made[7]; the negative U waves were associated with marked pressor response to exercise and disappeared 3 minutes thereafter, at the time when arterial pressure returned to pre-exercise levels. In subsequent exercise, when the pressor response to exercise was eliminated with sodium nitroprusside, negative U waves did not appear. It is possible that in patients with coronary disease, negative U waves following exercise are also a manifestation of the pressor effect of exercise and not of the associated coronary arterial disease.

Surawicz et al.[3] have noted, without reporting simultaneous arterial pressure measurements, that in some cases the faster heart rate was accompanied by a negative, and a slower rate by a positive U wave. In our study the polarity of the U waves was not influenced by the heart rate; in all patients in whom sodium nitroprusside was given, conversion of negative U waves occurred as a result of the arterial pressure fall and in spite of the slight increase in heart rate (fig. 2). Also in patients in whom spontaneous variations in the heart rate occurred, slowing resulted in change of the polarity of a negative U wave only when associated with a fall in arterial pressure. Similarly, positional changes did not influence the polarity of U waves unless the arterial pressure changed.

The four patients in whom negative U waves remained unchanged, despite lowering of arterial pressure, had serious cerebral and coronary arterial disease. Since it is well known that negative U waves also occur in normotensive patients with coronary arterial disease, it may be that vascular disease is an additional factor responsible for negative U-wave persistence in occasional hypertensive patients with well-controlled arterial pressure.

Lepeschkin[8] believed that the best explanation of the U wave is that it corresponds to potential differences produced during the descending limb of a negative afterpotential. Ferrero and Gay[9] suggested that a mechanical factor and an electrical one contribute to the genesis of the U wave. Furbetta et al.[10] concluded that U and T-U changes might be present in all cardiovascular diseases in which a hemodynamic abnormality places strain on the structures of papillary muscle. Although the mechanism by which negative U waves are produced is not clear, it is apparent from the results of our study that in hypertensive patients elevated arterial pressure is a contributing factor.

Summary

Direct correlation exists between arterial pressure levels and negativity of U waves in electrocardiograms of hypertensive patients; lowering of arterial pressure results in conversion of negative to positive U waves in the majority of hypertensive patients. Presence of negative U waves does not necessarily indicate organic myocardial changes or a grave prognosis; when their polarity remains unchanged following antihypertensive treatment, it may indicate unsatisfactory control of arterial pressure.

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Water

Of all the terrestrial agents by which the surface of the earth is geologically modified, by far the most important is water. We have already seen, when following hypogene changes, how large a share is taken by water in the phenomena of volcanoes and in other subterranean processes. Returning to the surface of the earth and watching the operations of the atmosphere, we soon learn how important a part of these is sustained by the aqueous vapor that pervades the atmosphere.

The substance which we term water exists on the earth in three well-known forms: (1) gaseous, as invisible vapor; (2) liquid, as water; and (3) solid, as ice. The gaseous form has already been noticed as one of the characteristic ingredients of the atmosphere. Vast quantities of vapor are continually rising from the surface of the seas, rivers, lakes, snow fields, and glaciers of the world. This vapor remains invisible until the air containing it is cooled down below its dewpoint, or point of saturation,—a result which follows upon the union or collision of two aerial currents of different temperatures, or the rise of the air into the upper cold regions of the atmosphere, where it is chilled by expansion, by radiation, or by contact with cold mountains. As the vapor is largely raised from the ocean surface, so in great measure it falls back agaain directly into the ocean. A considerable proportion, however, descends upon the land, and it is this part of the condensed vapor which we have now to follow. Upon the higher elevations it falls as snow, and gathers there into snow fields, which by means of glaciers, send their drainage towards the valleys and plains. Elsewhere it fall chiefly as rain, some of which sinks underground to gush forth again in springs, while the rest pours down the slopes of the land, swelling the brooks and torrents which, fed both by springs and rains, gather into broader and yet broader rivers that bear the accumulated drainage of the land out to sea. Thence once more the vapor rises, condensing into clouds and rain to feed the innumerable water channels by which the land is furrowed from mountain top to seashore.

In this vast system of circulation, ceaselessly renewed, there is not a drop of water that is not busy with its allotted task of changing the face of the earth.—GEIKIE, *Textbook of Geology*. London, 1903. 4th ed., Vol .I, p. 447.

Effects of Erythrol Tetranitrate and Amotriphene on Exercise Tolerance Tests in Angina Pectoris

By ARTHUR RUSKIN, M.D.

OBJECTIVE EVIDENCES for angina pectoris, in the absence of proved myocardial infarction or grossly abnormal electrocardiograms, are more or less limited to abnormal electrocardiographic changes induced by exercise or hypoxemia. Similarly, while termination or prevention of angina is notoriously unreliable in the evaluation of "coronary dilator" drugs, their effects on provoked abnormalities in the electrocardiogram may be considered objective, if not completely reliable.

Consequently, we compared the effects of sublingual erythrol tetranitrate (Cardilate*) and amotriphene (Myordil†) in selected patients with angina pectoris, who repeatedly showed positive Master exercise tests.

Material and Method

"Standardized" two-step exercise tolerance tests were performed.[1] Thirty-six patients with angina pectoris who had repeated (two to four) positive Master tests on placebos corresponding to the two drugs *(infra)* were selected for the study. Eight of them had had myocardial infarction 6 or more months previously, but showed no electrocardiographic residues beyond Q waves. None was receiving digitalis.

Our strict criteria of a positive exercise tolerance test were (1) flat S-T depressions totaling 3 mm. or more in leads I, II, III, V_2, and V_4 or (2) less marked S-T depressions, plus inversions of the T wave in leads I, II, V_2, and V_4 or with induced arrhythmias or conduction defects or both. Doubtful positive tests included borderline S-T depressions plus low negative changed to positive T-waves.‡

Sublingual erythrol tetranitrate 30 to 45 mg., oral amotriphene 50 to 75 mg., or a corresponding placebo was administered 45 to 60 minutes before the exercise test. These drug dosages were empirically found to cause the greatest number of reversals, i.e., in some cases smaller doses failed to reverse clearly placebo-positive Master tests. Identical drug and placebo tests were repeated from two to four times each on different days at approximately the same time in the afternoon. As a check on the longer acting nitrate, in three patients who had shown positive and three patients who had exhibited negative Master tests following the administration of erythrol tetranitrate the exercise tests were repeated within 5 minutes after 0.6 mg. of nitroglycerin by mouth.

In 20 cases clinical evaluation of the two drugs and placebos was done in 3-week periods each, arranged in varying Latin-square sequences and often repeated, especially in doubtful cases. Records exact as possible were kept by the patients of the number, kind, length, and severity of their pains, and the daily dosage of nitroglycerin tablets required. We thus had two comparative placebo and drug periods for cross-evaluation of their efficacy.

Results

Exercise tolerance tests positive following placebo were reversed by sublingual erythrol tetranitrate in 26 of 36 cases (72 per cent; figs. 1 and 2), while seven continued to be positive and three were doubtful (table 1). Three positive and three negative tests after the drug checked equally so after nitroglycerin (0.6 mg.).

Headache was a side effect in one quarter to one third of the cases, but it occurred infrequently if the patient was placed on a small dose first and this dose was gradually increased to the desired level. Excluding the large doses of the exercise test, it was mild, transient, and annoying in six of the 36 cases. Weakness, nausea, dizziness were fleeting and infrequent (table 2). Intermittent claudication was reduced on exercise in one case, but remained unchanged in another.

Oral Amotriphene resulted in six negative (fig. 2), four doubtful, and 26 positive (fig. 1) tests—a reversal of 16 per cent of the patients

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†WIN-5494, Winthrop Laboratories, New York, New York.

‡The latter occur most commonly in mentally disturbed patients in our experience.

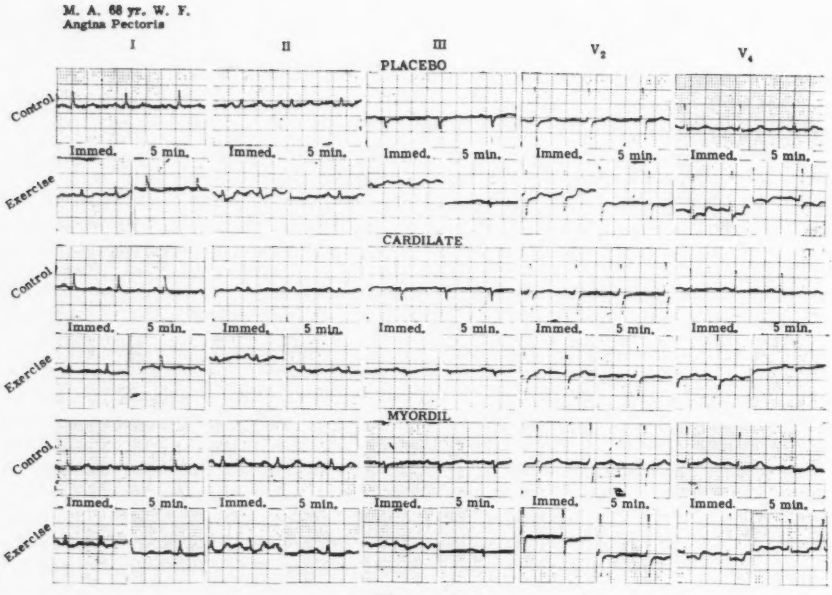

Figure 1

Positive exercise tolerance test reversed by erythrol tetranitrate (45 mg.), but not by amotriphene (75 mg.)—usual case.

exhibiting positive Master tests following placebos (table 1). Side effects from amotriphene were perhaps less frequent and severe, consisting primarily of headache, nausea, or dizziness on rare occasions (table 2). Intermittent claudication was unaltered in the two patients showing it.

In cases of reversal of a positive Master test by either drug, subjective symptoms on exercise such as precordial pain and dyspnea were also frequently reduced or eliminated. Daily anginal attacks on sublingual erythrol tetranitrate and oral amotriphene were respectively 0.92 and 0.94 versus placebo 2.17 and 1.94.

Ectopic beats, usually ventricular in origin, were infrequent in the control electrocardiogram, and often appeared or increased greatly on exercise after the placebos. Bigeminy and multifocal beats occurred in many cases. These arrhythmias were generally the same, e.g., in one case—paroxysmal ventricular tachycardia, on repeated exercise tolerance tests.

Premature beats produced or increased by the drug or on exertion were twice as frequent following erythrol tetranitrate as after

Table 1

Master Exercise Tests after Placebo, Erythrol Tetranitrate, and Amotriphene

	Placebos	Erythrol tetranitrate	Amotriphene
Positive	36	7	26
Doubtful	0	3	4
Negative	0	26	6

Table 2

Symptoms (Per Cent) Noted after Erythrol Tetranitrate, Amotriphene, and Placebos

	Erythrol tetranitrate	Amotriphene	Placebos
Headache			
Definite	24	6	—
Mild	14	12	12
Dizziness			
Definite	14	6	4
Mild	4	—	—
Weakness			
Definite	14	—	12
Mild	4	—	—
Nausea	14	6	—
Vomiting	4	—	—

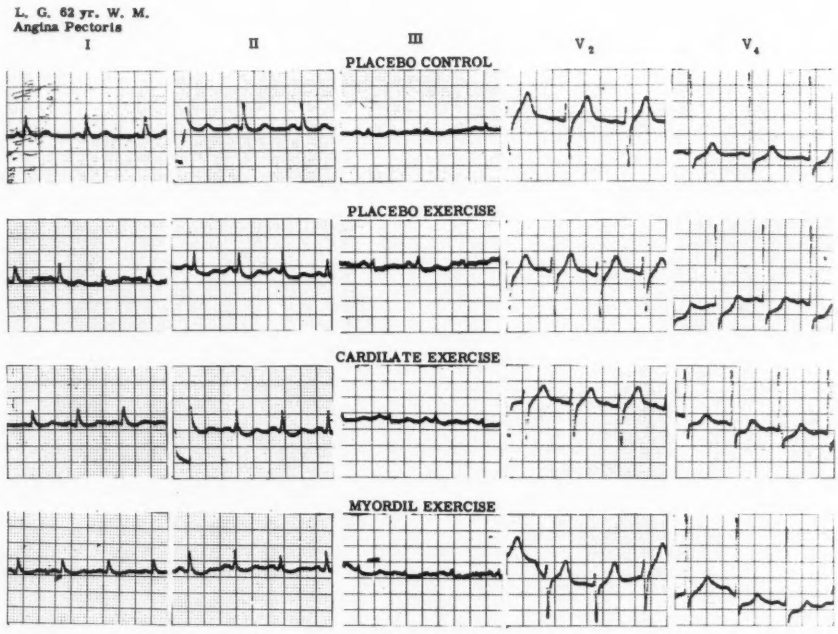

Figure 2

Equal reversal of positive exercise tolerance test by erythrol tetranitrate and amotriphene —unusual case.

amotriphene. Both drugs equally reduced or abolished premature beats on exercise. Similarly, in about 10 per cent the premature beats following the two drugs or the Master test remained about the same as in the tests following the placebos (table 3). Otherwise, the electrocardiograms were essentially unaltered by either drug.

Discussion

It is evident that sublingual erythrol tetranitrate is potent in reversing the electrocardiographic signs of coronary insufficiency in the majority of cases of angina pectoris (72 per cent). This corroborates previous reports of the efficacy of certain nitrites in coronary disease.[2-6]

Amotriphene, on the other hand, clearly reversed positive exercise tolerance tests in only 16 per cent. Experimentally[7-9] and clinically[10] it has been reported to have coronary dilator and anti-arrhythmic effects. It did decrease ectopic beats on exercise about as often as erythrol tetranitrate, but also produced them at times, though less frequently than erythrol tetranitrate. In any case, it would seem that premature beats as such should weigh little in the evaluation of a positive or negative Master test.

Although less definite, the evidence suggests that both erythrol tetranitrate and amotriphene reduce the number of anginal attacks in half. The parallelism between the objective and subjective findings for erythrol tetranitrate does not hold however for amotriphene.

Table 3

Ectopic Beats (Per Cent) in the Exercise Tolerance Tests Following Erythrol Tetranitrate and Amotriphene in Contrast to Placebos

	Induced or increased	Same as placebo	Abolished or decreased
Erythrol tetranitrate			
Drug alone	8	8	3
Exercise	13	10	13
Amotriphene			
Drug alone	3	12	0
Exercise	6	9	15

and the latter's clinical worth must remain *sub judice*. Other drugs, especially those producing sedation or monoamine oxidase inhibition, e.g., iproniazid, show the same disparity between apparent alleviation of angina and no objective evidence of abolition of coronary ischemia.[11, 12] This anti-anginal effect is, of course, hardly consonant with the resulting greater availability of catecholamines, which, despite coronary vasodilatation, produce relative coronary ischemia.

Headache from erythrol tetranitrate was in our experience no more frequent than from nitroglycerin. It recurred infrequently when the dose was reduced and gradually increased to the same level. In fact, the large doses (30 to 45 mg., which are two or three times the usual dose) employed in the exercise tolerance tests did not cause headache in some cases. Only two patients, not included in the 20 cases rotated on the various regimens, were unable finally to tolerate 15 mg. doses of the drug. Nor were angina pectoris or adverse electrocardiographic effects produced or aggravated by the large test doses of erythrol tetranitrate, whereas failure of coronary dilatation[13, 14] or severe coronary insufficiency[15] has occurred from heavy doses of the fast-acting nitroglycerin, in part as a result of hypotensive ischemia.

Summary

Sublingual erythrol tetranitrate is a potent drug in counteracting coronary insufficiency, as evidenced by reversal of positive electrocardiographic exercise tolerance tests in 72 per cent of 36 cases and reduction of anginal attacks in them by more than 50 per cent.

Comparative studies with amotriphene indicate some subjective alleviation of angina, but objective reversals of the electrocardiographic effects of exercise in only 16 per cent of the cases.

Side effects of erythrol tetranitrate, particularly headache, are seen in a minority of cases and are often circumvented by starting with a small dose and gradually increasing it as necessary.

Alleviation of ectopic beats on exercise occurred equally in a minority of cases on the two drugs.

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Isolated Ventricular Septal Defect of the Persistent Common Atrioventricular Canal Type

By HENRY N. NEUFELD, M.D., JACK L. TITUS, M.D., JAMES W. DUSHANE, M.D., HOWARD B. BURCHELL, M.D., AND JESSE E. EDWARDS, M.D.

IN RECENT YEARS certain electrocardiographic patterns have come to be associated with the congenital cardiac malformation called "persistent common atrioventricular canal."[1-4] Experience has shown, however, that the electrocardiographic features are not specific for that malformation. They may be observed also in cases in which both great vessels arise from the right ventricle without pulmonary stenosis,[5] in certain cases of ventricular septal defect,[6] in some cases of atrial septal defect of the ostium secundum type,[7] and in certain cases of acquired heart disease. The same features are observed in cor triloculare biventriculare (common atrium), but this malformation may be considered a variant of persistent common atrioventricular canal.[8]

The purpose of this study was to review those cases of anatomically proved ventricular septal defect occupying the position of the ventricular component of the defect in the complete form of persistent common atrioventricular canal. An answer was sought to the question of whether this anatomic character of the ventricular septal defect could account for the electrocardiographic findings, namely, early QRS vectors being directed to the left and the QRS vectors in the frontal plane describing a counterclockwise loop and lying mostly superior to the isoelectric point.

Search of the clinical, surgical, and pathologic files of the Mayo Clinic (involving 60 necropsy specimens and more than 300 cases of ventricular septal defect observed at operation) yielded 15 cases of isolated ventricular septal defect of the anatomic AV commune type (table 1). In six cases the anatomic nature of the defect was studied only at the time of cardiotomy under the conditions of extracorporeal circulation. In the other nine cases necropsy specimens were available for study. Each specimen was examined by conventional means; in four cases the specimens were studied also by examining serial sections of the conduction system.

Pathologico-anatomic features of ventricular septal defects have been studied and described, among other investigators, by von Rokitansky,[9] Becu and associates,[10] Kirklin and co-workers,[11, 12] and Warden and associates.[13] Kiely and associates[14] emphasized the possibility that isolated ventricular septal defects of the common atrioventricular canal type may occur with or without involvement of the atrioventricular valves.

Pathologic Features

In the group of 15 cases described in this paper (cases 1 to 15, table 1), the pathologic features (figs. 1 and 2) were as follows. From the right ventricular aspect, the ventricular septal defect extended anteriorly to the crista supraventricularis. A part, at least, of the membranous septum was identifiable and formed the anterosuperior boundary of the defect. The defect did not extend anteriorly beyond the papillary muscle of the conus. The posterior edge of the defect extended more dorsally than does the more common type of defect, and its entire superior edge lay immediately beneath the tricuspid ring. From the left ventricular view, the defect was positioned beneath the membranous portion of the

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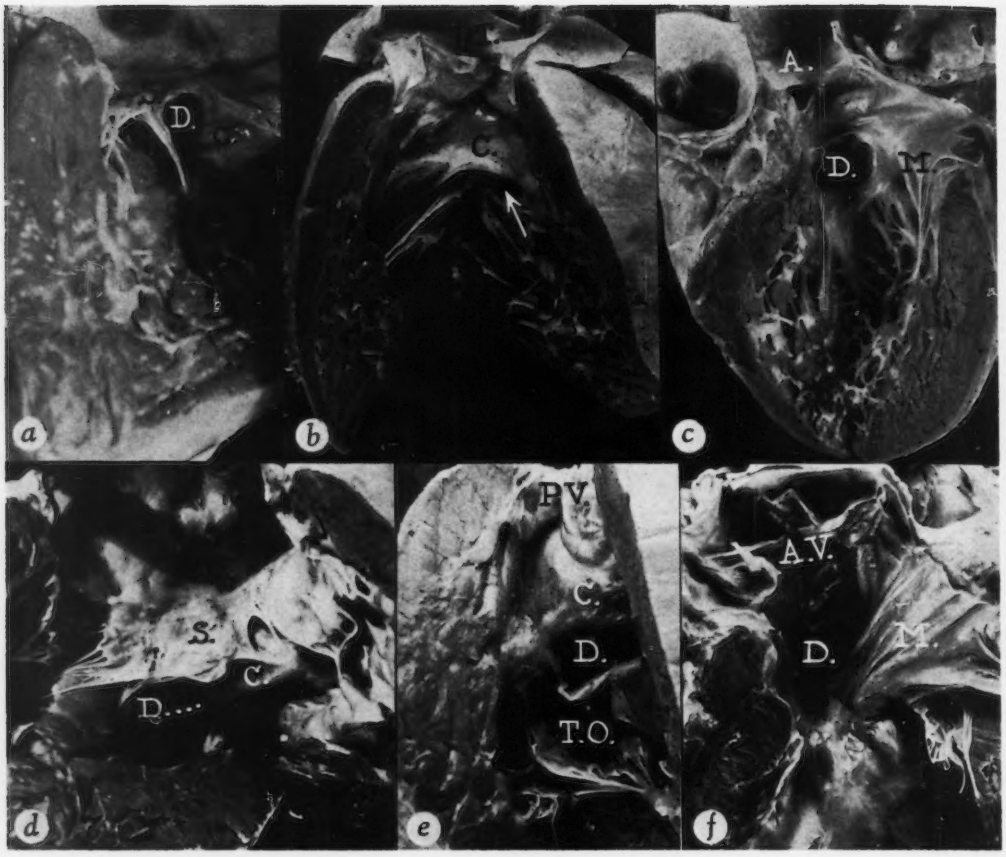

Figure 1

Case 2. a. *Right atrium and ventricle. Ventricular septal defect (D.) is overhung by septal leaflet (S.) of tricuspid valve. Although no striking cleft is apparent in tricuspid valve, minor defect appears to be present in tissue between septal leaflet and anterior leaflet. Chordae of septal leaflet of tricuspid valve are deficient. Anterosuperior extremity of defect is formed by crista supraventricularis (C.)* b. *Right ventricular aspect and pulmonary trunk (P. T.). Ventricular septal defect (D.) abuts on inferior aspect of crista supraventricularis (C.).* c. *Left ventricular aspect. Ventricular septal defect (D.) lies in front of anterior leaflet of mitral valve (M.) and involves considerable amount of muscular part of ventricular septum where it forms wall of outflow tract of left ventricle. Beneath aortic valve is membrane representing membranous portion of ventricular septum, which forms upper boundary of defect. The mitral valve was devoid of clefts. Case 3.* d. *Tricuspid valve and adjacent structures. Beneath septal leaflet of tricuspid valve (S.) is ventricular septal defect (D., pointing to probe in defect). Anterosuperior extremity of defect is bounded by crista supraventricularis (C.). Tricuspid valve is devoid of clefts.* e. *Right ventricular aspect and pulmonary valve (P. V.). Ventricular septal defect (D.) lies between septal leaflet of tricuspid valve below and crista supraventricularis above (C.). At border of defect crista supraventricularis has an arch-shaped deformity. This corresponds to position of left ventricular aspect of defect. Right ventricular hypertrophy is pronounced. (T. O. = tricuspid orifice.)* f. *Left ventricular aspect. In front of anterior leaflet of mitral valve (M.) is large ventricular septal defect (D.). Defect extends for considerable distance into anterior part of muscular portion of ventricular septum, which forms wall of outflow tract of left ventricle. Aortic valve (A. V.) does not form immediate boundary for defect; instead, a fragment of membranous portion of ventricular septum is attached to aortic valve and forms upper boundary of defect.*

ventricular septum. The upper edge of the defect was separated from the aortic leaflets by the membranous portion of the ventricular septum or by the musculature that corresponds to the crista supraventricularis (figs. 1 and 2). In contrast to what is found in the common type of ventricular septal defect, the aortic valve did not form a boundary of the defect in the 15 cases considered herein.

In two cases (cases 1 and 6, table 1) a cleft was found in the septal leaflet of the tricuspid valve. In two cases (cases 7 and 9) a cleft was present in the anterior leaflet of the mitral valve. In four cases (cases 11 to 14) both the septal leaflet of the tricuspid valve and the anterior leaflet of the mitral valve showed a deformity or a cleft. In three cases there was an associated atrial septal defect at the fossa ovalis, and in one case there was no cleft, but both atrioventricular valves were continuous through the defect. In no case was an atrial septal defect of the ostium primum type present.

These findings indicate that the degree of the deficiency varied. In some cases the deficency occurred only in the junction of the lower portion of the atrioventricular endocardial cushions; the remainder of the region of the atrioventricular canal had developed normally. In other cases the deficiency apparently included the atrioventricular valves but not the atrial septum.

Embryology

The complete and partial varieties of persistent common atrioventricular canal—their embryology, pathology, and clinical picture—are now well known.[15-20] It is also known that in some cases only an isolated malformation of the atrioventricular cushion may be found. This malformation may exist as an isolated ostium primum, as an isolated cleft of the mitral or tricuspid valve or of both, and as an isolated ventricular septal defect with or without cleavage of the atrioventricular valves.[14]

Kramer[21] demonstrated that, embryologically, the endocardial cushions make a specific contribution to the closure of the ventricular septum. The atrioventricular cushions at the base join the muscular part of the ventricular septum to obliterate the interventricular communication in this region. Final closure of the embryonic interventricular foramen results from fusion of elements of the endocardial cushions of the atrioventricular canal, the conus septum, and the endocardium of the muscular septum.[15, 21] The ventricular septal defect of the type described herein appears to result from failure of fusion of these three elements. Failure of fusion not only allows a defect to remain, but it also deprives the developing muscular septum of its anchors. As a result of the mechanical tensions of the growing heart, the unanchored muscular septum is pulled away from the atrioventricular region, causing enlargement of the defect.

If we are correct in reasoning that the ventricular septal defect under consideration is primarily a result of deficiency of atrioventricular cushion, it seems logical to consider the defect a variant of persistent common atrioventricular canal. The anatomic position of the defect, and, as will be shown, the similarity of the unusual excitatory pattern in the electrocardiogram as compared with electrocardiographic phenomena found in common atrioventricular canal, as well as the similarity in the conduction system and associated lesions in the atrioventricular valves, support our assumption.

The Conduction System

Mönckeberg[22, 23] found that in patent foramen ovale and ventricular septal defect, the location and distribution of the atrioventricular node, bundle of His, and bundle branches were normal. He and Keith[24] also found that the bundle always passed below the defect. Morison,[25] in a report of a case of a malformed heart with atrial septal defect, which, from the illustrations, appeared to be of the ostium primum type, found the atrioventricular node displaced posteriorly and below the coronary sinus. The fibers of the bundle split into an abortive left branch, which failed to reach the left ventricle, and a large right branch, which divided to supply

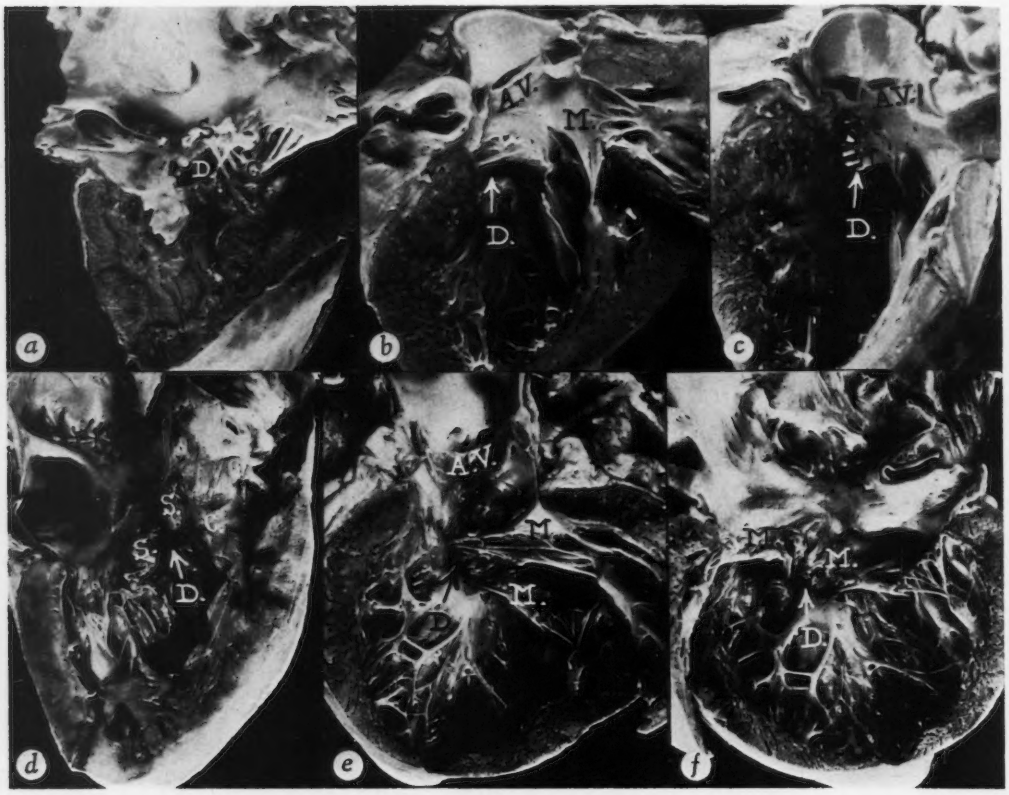

Figure 2

Case 9. a. *Right side of heart. Ventricular septal defect (D.) is overhung by septal leaflet of tricuspid valve (S.), which has been partly retracted upward to expose defect. Chordae from under aspect of atrioventricular valvular tissue are inserted in lower edge of defect. Anterosuperior extremity of defect is formed by crista supraventricularis (C.).* b. *Left ventricular aspect. Ventricular septal defect (D.) cuts into muscular portion of outflow tract of ventricular septum. Beneath aortic valve (A. V.) is membranous portion of ventricular septum, which is continuous with anterior leaflet of mitral valve (M.). Chordae from anterior aspect of atrioventricular valvular tissue insert into edges of ventricular septal defect, as shown in* a. c. *Close-up view of ventricular septal defect (D.) from left ventricular aspect, showing extension of chordae across ventricular septal defect and at same time extensive deficiency of anterior portion of muscular part of ventricular septum in this region. (A. V. = aortic valve.) Case 14.* d. *Right side of heart. Beneath septal leaflet of tricuspid valve (S.), which is cleft, is ventricular septal defect (D.). Anterosuperior boundary of defect is formed by crista supraventricularis (C.).* e. *Left ventricular aspect. Anterior leaflet of mitral valve (M.) is cleft. Chordae from edges of cleft insert into anterior wall of ventricular septal defect (D.). Aortic valve (A. V.) lies above defect and is separated from it by elements of membranous portion of ventricular septum.* f. *Left atrium and left ventricle. Ventricular septal defect (D.) is overhung by cleft of anterior leaflet of mitral valve (M.). Chordae from edges of crest of mitral valve insert into anterior wall of ventricular septal defect on its right ventricular aspect.*

both the right and left sides. Wallgren and Winblad,[26] studying a case of persistent ostium primum associated with complete atrioventricular block, were unable to find continuity between the atrioventricular bundle and the node. Lev[27] found in four cases of the complete variety of persistent common atrioventricular canal that the conduction system presented a fairly common pattern. The sinoatrial node was normal. The atrioventricular node was displaced posteriorly, originating mainly from the posterior wall of the atrium. In the absence of a well-formed atrial and ventricular septum, the atrioventricular bundle was displaced posteriorly, skirting the lower margin of the defect. In some instances the right bundle branch gave off several strands rather than continuing as a single trunk.

In two of our cases (cases 1 and 5) the conduction system was studied histologically by making serial sections of blocks taken from the region of the atrioventricular junction; the posterior limit of the blocks was approximately the ostium of the coronary sinus, and the anterior limit was the crista supraventricularis. The blocks included approximately 1 cm. of interatrial septum superiorly and 2 cm. of interventricular septum inferiorly. By study of serial sections of such blocks, the locations of the atrioventricular node, common atrioventricular bundle (bundle of His), and right bundle branch could be determined. This method is similar to that used in other histologic studies of the conduction system (fig. 3).[27]

The atrioventricular node appeared to be in its usual location. The bundle arose from the anterior extension of the node and penetrated the central fibrous body in the usual fashion. This course placed the most anterior extension of the bundle just above the posterosuperior angle of the ventricular septal defect. At this point the conduction fibers turned downward posteriorly behind the defect and followed the posterior edge of the ventricular septal defect in the form of an arc (fig. 3). These abnormalities are explicable in the light of what is known of the embryogenesis of the conduction system. In the mammal the atrioventricular node and bundle originate from the posterior part of the musculature of the atrial canal that lies

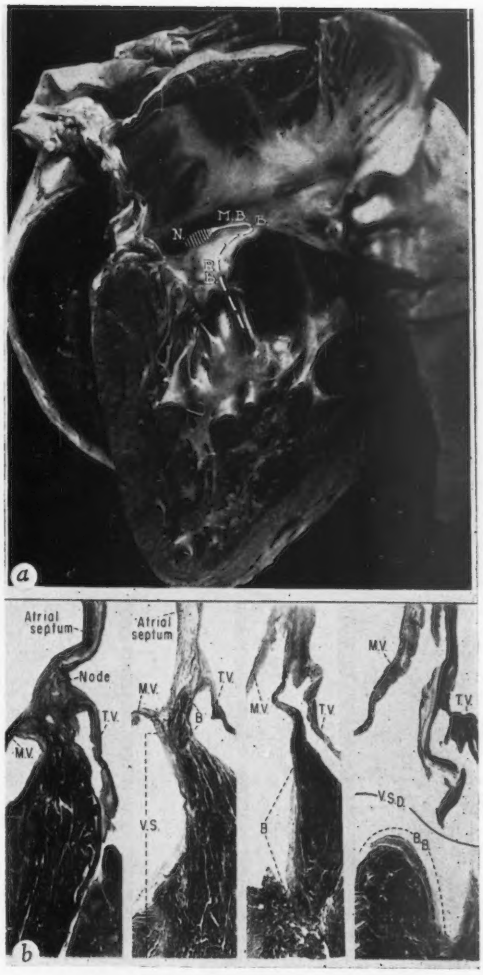

Figure 3

a. *Interior of right side of heart; conduction system. Atrioventricular node (N.) is in usual location. Main bundle (M. B.) arises from ventral extent of node and runs to branching point (B.); here right bundle (R. B.) begins and continues in an arc dorsally to defect.* b. *Photomicrograph of conduction tissue. M. V. = mitral valve; T. V. = tricuspid valve; B. = bundle; B. B. = branching bundle; V. S. = ventricular septum; V. S. D. = ventricular septal defect.*

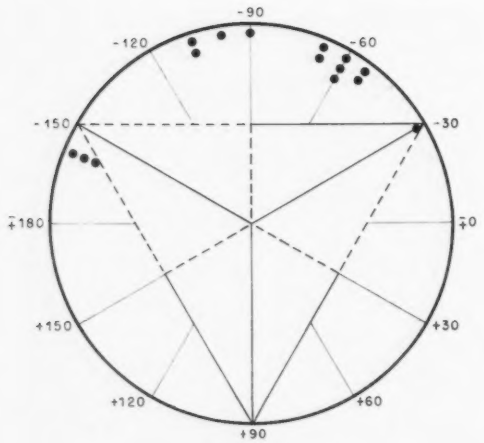

Figure 4

Diagram of manifest mean electrical axis of QRS complexes in 15 cases (●).

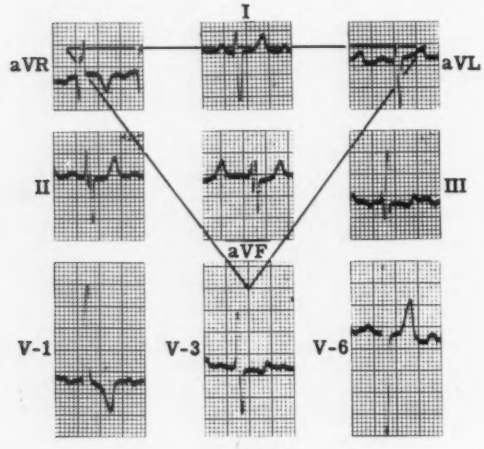

Figure 5

Electrocardiogram in case 14. (See table and fig. 2d, e, and f.)

behind the posterior endocardial cushion. The ventricular septal defect may be looked on as resulting from lack of fusion of atrioventricular endocardial cushion tissue with the muscular part of the ventricular septum. As the ventricular septal defect grows in size with growth of the heart, the bundle of His, which initially was apparently in a normal position, becomes displaced posteriorly by the enlarging defect. Thus, our findings with regard to the conduction tissue in the variant of persistent common atrioventricular canal considered herein are similar to those found in the fully developed stage of the malformation as reported by Lev.[27]

Electrocardiographic Findings (Table 1)

Rhythm. In one case (case 3) there was an ectopic atrial rhythm. In the other 14 cases normal sinus rhythm was recorded, with multiple premature ventricular beats occurring in two of these.

P-R Interval. In all 15 cases the P-R interval could be measured. In seven cases it was considered to be normal, and in eight cases the value was at the upper limit of normal or considered to be prolonged in relation to heart rate and age[28] (table 1).

P Wave. Alteration of either the P wave or the QRS complex, or both, suggestive of enlargement of the right atrium, was found in one case (case 1). In two cases (cases 7 and 9) configuration of the P wave was indicative of enlargement of the left atrium. In another case (case 2) the alteration was suggestive of enlargement of both atria, and in the remaining five cases that demonstrated anatomic evidence of malformed atrioventricular valves, the changes in the P wave were not diagnostic.

The electrocardiographic signs of enlargement of the left atrium or right atrium or both were compatible with the anatomic findings of mitral insufficiency or tricuspid insufficiency, or both, as noted at necropsy or at operation. In two cases (cases 7 and 12) wedge pressures were obtained; they showed increased pressure (mean pressure of 20 and 26), with the V waves being prominent. In case 12, normal P waves were seen on electrocardiograms.

QRS Complex. The mean electrical axis of the QRS complex in the frontal plane was estimated in all cases. The mean electrical axis lay between −30° and −160° (table 1 and fig. 4). The duration of QRS was 0.07 second or less in five cases, between 0.07 and 0.08 second in five cases, and greater than 0.08 second in five cases. Vector analysis of the QRS complex in the frontal plane (table 1 and figs. 5 to 7) revealed in all cases that the

Table 1

Electrocardiographic Findings in Fifteen Cases of Ventricular Septal Defects of the Persistent Common Atrioventricular Canal Type

Subject	Age and sex	Heart rate	P waves	PR interval (II), second	QRS (II), second	QRS axis	Frontal vector loop	Lead V_1* QRS pattern	R	S	T	Lead V_6* Q	R	S	T	Lead I T	Hemodynamic data: Pressure in right ventricle	Shunts: Left-to-right†	Shunts: Right-to-left‡
1	19 yr. F	100	Prominent in II, III, V_1, V_2	0.16	0.08	—110°	C§	rR's	r = 2 R′ = 25.0	2.0	—	0.5	8.0	11.0	+	+	126/0	39% (O_2)	27% (O_2) 59% (air)
2	7 yr. F	95	Notched in I, II, III, aV_F, V_1	0.28	0.07	—160°	C Figure-of-8				—				—	+	95/5		
3	24 yr. M	67 (Ectopic atrial rhythm)	Normal	0.24	0.10	— 60°	C	rsR′	r = 2.0 R′ = 23.0	2.0	—	7.0	23.0	10.0	—	—	113/6	72% (air)	20% (air)
4	24 yr. M	74	Prominent in II, III	0.16	0.09	— 50°	C	rR′	r = 1.0 R′ = 18.0		+	2.0	25.0	13.0	+	+	109/3	64% (air)	18% (air)
5	7 yr. M	96	Prominent in II, aV_F, V_1	0.18	0.07	—100°	C	RS	20.0	13.0	+	4.0	22.0	20.0	+	+	80/0		
6	28 yr. F	82		0.16	0.10	— 60°	C	rSr′	r = 2.0 r′ = 2.0	11.0	—+		10.0	3.0	+	—	25/0	52% (air)	
7	1-2/3 yr. F	130	Prominent in I, II	0.14	0.07	—160°	C	Rs	25.0	5.0	—	6.0	32.0	1.0	—	—	60/0	W.P.‖ 25/10	
8	5-1/2 yr. F	112	High in II, III, aV_F	0.20	0.09	— 70°	C	Rs	21.0	2.0	—		23.0	8.0	—+	—	74/0		
9	11 mo. M	138	High in I, II, V_1, aV_F	0.16	0.07	— 50°	C	RS	14.0	10.0	—	3.5	23.0	18.0	—+	—	87/3	33% (air)	43% (air)
10	5 yr. F	100	Normal	0.17	0.08	— 90°	C	RS	11.5	12.0	+	2.0	14.0	7.0	—	—	86/3		
11	5-1/2 yr. F	106	Notched in II, III, aV_F	0.21	0.08	— 30°	C	rS	8.5	14.5	—	2.0	13.0	1.0	—	—			
12	11 yr. F	95	Normal	0.16	0.08	— 60°	C	rsR's′	r = 2 R′ = 6	s = 10 s′ = 3	+	1.5	25.0	9.0	+	—+	56/6	30% (air) W.P.‖ 30/20	20% (air)
13	2 yr. F	108	Notched in I, II, III, aV_F, V_1	0.14	0.08	— 70°	C	rsR's	r = 1.5 R′ = 26.0	3.0	—+	0.5	11.0	5.0	+	—+	120/14		
14	7 yr. F	90	Normal	0.16	0.09	—160°	C Figure-of-8	rsR′	r = 1.5 R′ = 22		—	0.5	15.0	21.0	+	+	100/5	70% (O_2) 35% (air)	21% (O_2) 54% (air)
15	2 mo. M	123	Normal	0.10	0.06	—100°	C	rsR's′	r = 1.0 R′ = 17.0	s = 1.0 S′ = 1.5	+	0.5	20.0	20.0	—	—			

*Values for Q, R, and S are in millimeters.

†Expressed as per cent of total pulmonary flow.

‡Expressed as per cent of systemic flow.

§C = Counterclockwise.

‖W.P. = Wedge pressure.

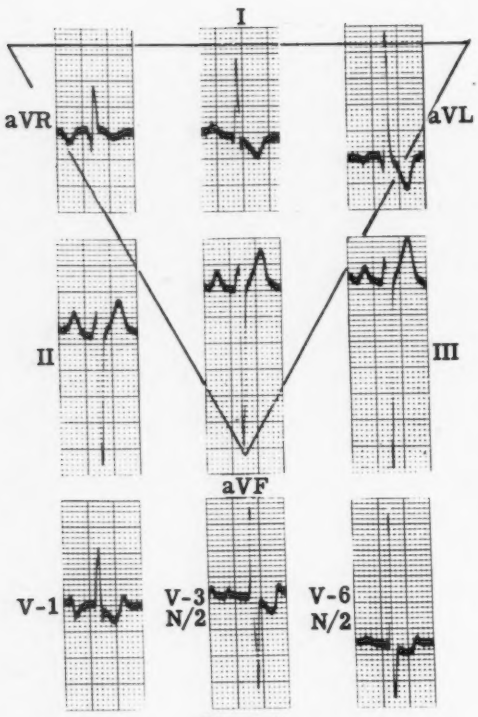

Figure 6

Electrocardiogram in case 8, in which anatomic diagnosis was proved at operation. (See table 1.)

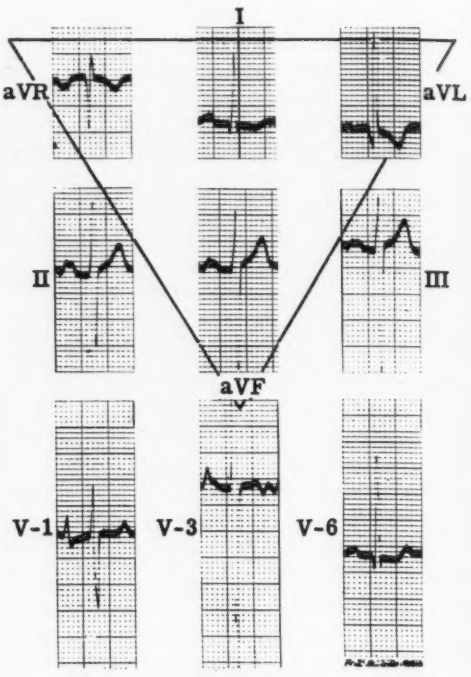

Figure 7

Electrocardiogram from case 11, in which anatomic diagnosis was proved at operation. (See table 1.)

instantaneous vector advanced in a counterclockwise direction and was mainly superior to the isoelectric point. In two cases (cases 2 and 14, fig. 5) the vectorcardiogram showed a narrow figure-of-eight configuration of the QRS loop placed horizontally across the isoelectric point, with the initial loop rotating in a counterclockwise direction.

Chest leads were obtained in 14 of the 15 cases. Various configurations of the QRS complex in lead V_1 were found. In eight cases the configuration of QRS complexes in lead V_1 (rsR′, rSr′) was suggestive of "diastolic (or volume) overloading" of the right ventricle. In the remaining cases the configuration of the QRS complex was RS. The ratio of R to S in lead V_1 was indicative of overloading of the right ventricle in 10 cases.

In lead V_6, two different types of QRS configurations were observed: RS in two cases and QRS in 12. In only three cases was the ratio of R to S in lead V_6 equal to or less than 1 (cases 1, 14, and 15). One of these three was the case of a 2-month-old child. In the remaining cases the ratio of R to S in lead V_6 was greater than 1.

T Wave. The T wave was found to be negative in lead I in eight cases (table 1, figs. 6 and 7). In two cases it was biphasic; the meaning of this finding is not clear to us. These changes in lead I were found to be rare in an electrocardiographic-anatomic study of 50 cases of the usual type of ventricular septal defect,[29] and they are not emphasized in the literature.

Special Anatomic Features

The ventricular septal defect described herein and considered to be of the persistent common atrioventricular canal type has an anatomic peculiarity: the upper edge of the defect is not bordered by muscle but rather by the tricuspid ring. There are other defects of the ventricular septum that, because of their location, resemble the one described; however,

these defects are completely surrounded by muscle and so have a band of muscle separating them from the tricuspid ring.

Findings in Two Related Cases

Special study of two cases was of interest from the point of view of the conduction tissue and the electrocardiograms, although they did not fall into the category of the 15 cases presented in this paper. In one case the pathologic examination revealed two defects (fig. 8). One was located posteriorly, close to the tricuspid ring, and the other was found more anteriorly; a band of muscle surrounded the posterior defect and separated it from the anterior one. Study of the conduction system revealed that the bundle of His and its right branch lay between the two defects, in the muscle separating them (fig. 8). The electrocardiogram in this case showed the usual pattern found in ventricular septal defect. The mean manifest electrical axis of the QRS complex was + 100°, with a clockwise loop of the QRS in the frontal plane on the scalar electrocardiogram.

In the second case a large ventricular septal defect was located posteriorly. A band of musculature was found between the ventricular septal defect and the tricuspid ring (fig. 9). Although in this case the defect was unusually positioned and suggested the atrioventricular canal type, careful observation proved it to be of the muscular type of defect. Study of the conduction system showed that the right bundle lay ventral to the defect, in its usual position. The electrocardiogram showed a mean electrical axis of the QRS complex of + 100° and a clockwise loop in the frontal plane. There were signs of right ventricular overloading and, in some cases, of left ventricular overloading as well.

Discussion

The electrocardiographic findings in our 15 cases have been thought by some authors to be virtually diagnostic of persistent common atrioventricular canal. This study indicates that such electrocardiograms are also characteristic of isolated ventricular septal defect of the types described in this paper. They have also been noted in cases having both great vessels arising from the right ventricle without pulmonary stenosis,[5] occasionally in other types of ventricular septal defect,[6] and in some cases of atrial septal defect of the ostium secundum type;[7] opportunity has not yet been afforded for careful histologic study of the conduction system in the latter conditions. This defect is different anatomically and hemodynamically from the so-called common persistent atrioventricular canal. It differs surgically also, the surgical risk in these cases apparently being higher than in the usual type of ventricular septal defect.

Figure 8

Interior of right side of heart with two ventricular septal defects. One defect is located more posteriorly, close to tricuspid ring but surrounded by band of muscle. Other defect is more anteriorly positioned. Dotted lines represent conduction system, which was studied in this case. As shown here, bundle of His and its right branch lay between the two defects (ventral to the dorsal defect) in muscle separating them. (This case is not one of the 15 described in this paper.)

The electrocardiographic findings were striking. In all instances the mean electrical axis of the QRS complex lay above the isoelectric point, with a vector loop directed in a counterclockwise direction; the chest leads indicated right ventricular "diastolic (volume) overloading" or right ventricular hypertrophy. These electrocardiographic changes

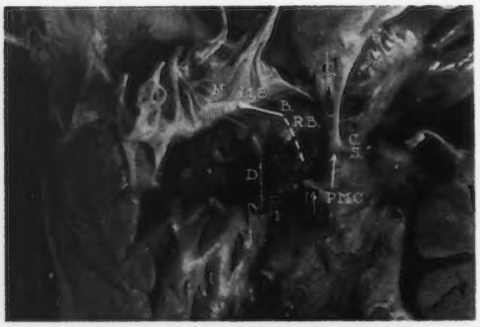

Figure 9

Interior of right side of heart. (This case is not one of the 15 described in this paper.) N. = node; M. B. = main bundle of conduction; B. = branching point (dotted lines); R. B. = right bundle; P. M. C. papillary muscle of conus; C. S. = crista supraventricularis; D. = ventricular septal defect.

have not been described often in reports on ventricular septal defect. Toscano-Barboza and DuShane[30] found similar electrocardiographic features in nine of 59 cases. Char and associates[31] and Keith and co-workers,[32] among other investigators, also reported that these electrocardiographic patterns were rare in cases with ventricular septal defect; these investigators did not correlate the electrocardiographic findings with the anatomic position of the defects.

Taussig,[33] Blount and associates,[18] and Toscano-Barboza[1] and co-workers, discussing the importance of electrocardiographic findings in persistent common atrioventricular canal, described similar electrocardiographic phenomena. Subsequently other authors[34-37] described the same changes.

Regarding the cause of the aberrant excitation recorded on the electrocardiogram in persistent common atrioventricular canal, there has been some controversy over the possible role that mitral regurgitation plays.[38] Certain factors militate against the importance of mitral regurgitation. Thus, Burchell and associates[2] pointed out that electrocardiograms of newborn infants with defects of the atrioventricular canal already show the characteristic tracing. Furthermore, the coexistence of pulmonary stenosis does not change the typical excitatory phenomena.[2, 37, 39] And electrocardiographic findings do not correlate either with the size of the left ventricle or with the degree of mitral regurgitation estimated during operation.[2]

Toscano-Barboza and co-workers[1] assumed that the position of the "defect at the top of the ventricular septum" causes the alteration in excitation. In 1959 Ellis and associates[5] described five cases of common atrium in which the electrocardiographic findings were similar to those found in persistent common atrioventricular canal. Neufeld and associates[5] found similar electrocardiographic changes in patients with origin of both great vessels from the right ventricle without pulmonary stenosis. All these findings, together with the electrocardiographic patterns of alteration in excitation in cases of ventricular septal defect of the atrioventricular type, suggest the presence of a congenital anomaly or distortion of the conduction system.

Burchell and associates'[2] opinion, based on recordings of electrocardiographic potentials from the cavities and surfaces of the ventricles, is that the different orientation of the advancing fronts of depolarization is the result of congenital absence of a portion of the left bundle-branch system.

A factor to be considered is the constant finding of a change in the anatomic location of the conduction system in cases of persistent common atrioventricular canal, as described by Lev[27] and as observed in our cases (fig. 3). The bundle retains its primitive relationship to the posterior endocardial cushion and is mislocated posteriorly, skirting the posterior rim of the defect. The elongation and looping of the bundle around the defect (fig. 3) are congenital anomalies, and the developmental basis of these anomalies of the conduction system is probably the same. Such anomalies may be the cause of the alteration in excitation that gives the characteristic pattern on the electrocardiogram.

Summary

Among 60 necropsy specimens of isolated ventricular septal defects and more than 300 cases of ventricular septal defect observed at

operation, 15 cases demonstrating unusual anatomic positions of the defect were found. The ventricular defect differed from the ordinary ventricular septal defect in that it usually occupied the position of the ventricular component of the defect in persistent common atrioventricular canal. For this reason it was named *ventricular septal defect of the persistent common atrioventricular canal type.*

Deformities of one or both atrioventricular valves were common (nine of 15 cases). No atrial septal defects of the ostium primum type were present. Anatomic studies of the conduction tissue revealed that this tissue skirted the posterior and inferior aspects of the ventricular septal defect and that, as in persistent common atrioventricular canal, the course taken by the conduction tissue was unusually long, as a result of the peculiar posteroinferior position of the lower edge of the defect.

The electrocardiographic features were striking. In all cases the mean electrical axis of the QRS lay above the isoelectric point; the vector loop obtained in the frontal plane from the scalar electrocardiogram was directed counterclockwise, and its main mass was above the zero line. In addition, in all cases there were signs of right ventricular overload, and in some cases of left ventricular overload as well.

Electrocardiographic findings of this pattern have been thought by some authors to be diagnostic of persistent common atrioventricular canal, but we observed that they also occurred in each of the cases of isolated ventricular septal defect of the variety described herein. We recognize that in the usual variety of ventricular septal defect this electrocardiographic pattern occurs, but it does so uncommonly. We have not studied its exact incidence. The anatomy, hemodynamics, and surgical considerations are different in cases with this defect from those with persistent common atrioventricular canal. The surgical risk in these cases has been higher than that in the usual type of ventricular septal defect.

In the discussion of the electrophysiologic theories that seek to explain the unusual electrocardiographic patterns in this group of cases, a new theory is offered, based on studies of the conduction system. In our opinion, the different orientation of the advancing fronts of depolarization is the result of congenital displacement of the bundle of His in its relation to the ventricular septal defect.

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The Prognosis of Essential Hypertension Treated Conservatively

By MAURICE SOKOLOW, M.D., AND DOROTHEE PERLOFF, M.D.

THE PROGNOSIS of essential hypertension is variable; some patients remain asymptomatic for years, while others develop disabling or fatal complications. What are the clues that enable the physician to predict the course in a particular patient? What is the natural history of hypertension treated not with modern drugs but with agents known in Janeway's and Osler's time? This information is necessary in order to evaluate the effect of drugs in prolonging life in essential hypertension.

In 1946, when the present study began, enthusiasm for sympathectomy as definitive therapy for essential hypertension[1, 2] was at its height. Yet at this time a review of the literature revealed no single, complete, detailed, prospective study of the natural history of untreated hypertension with which to compare the results of sympathectomy. A number of excellent articles described various phases of prognosis,[3-5] but important details were often omitted. For instance, the source of the sample could not always be determined: whether hospitalized patients or clinic outpatients, whether selected cases chosen retrospectively or consecutive patients followed prospectively. In the various series, the age of the patients, as well as the proportion of men and women, differed widely. In Rasmussen and Bøe's series,[6] for example, only 10 per cent of the patients were under 50 years, while in Perera's 250 cases,[7] the average age was 36 years. The length of the follow-up period was often expressed in terms of average duration rather than as a definite minimum number of years, and in some studies only 50 per cent of patients were followed for the entire period. Some samples were weighted with mild cases; in others, the preponderance of patients had severe hypertension. For instance, 9 per cent of Bechgaard's patients had normal blood pressures on repeat examination, indicating that they were vascular hyperreactors,[8] whereas 67 per cent of Keith and Wagener's series had malignant hypertension.[9] In some studies the degree of involvement of vital organs was not definitely stated; for example, the degree of cardiac enlargement or hypertrophy as determined by electrocardiograms when the patients were first seen. The incidence of vascular complications varied widely in the different studies. Thus, cardiac involvement was noted in 70 per cent of Rasmussen and Bøe's series,[6] in 35 per cent of Peet and Isberg's patients,[10] but in only 20 per cent of Bechgaard's patients.[8]

In addition, contradictory statements were made regarding the value of blood pressure readings. Janeway stated that a single blood pressure reading was of no value in prognosis because of the day-to-day variations.[11] Actuarial Society data, on the other hand, report that the rate of mortality increased progressively with increasing levels of casual blood pressure,[12] and Bechgaard,[8] commenting on the increased incidence of cardiac hypertrophy with increasing levels of casual blood pressure, concluded that even the first outpatient reading had significance for the group as a whole. Individual exceptions were cited, such as Ehrstrom's 20 patients who survived 10 years despite blood pressure levels exceeding 200 mm. Hg.[13]

The mortality in different series also showed

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Table 1

Criteria for Classification of Severity of Hypertension

Severity of hypertension	Blood pressure (mm. Hg)	Fundal classification	Heart size (x-ray)	Electro-cardiogram	Congestive heart failure	Renal function
Class I	Grade I (150-200/ 90-120)	K-W I	Grade I (0-10%)	Normal, borderline, LVH I and II	0	Normal
Class II	Grade II (200-250/ 110-130)	K-W II	Grade II (11-20%)	LVH III or no characteristic pattern	0	Normal
Class III	Grade III (over 250/ 130)	K-W III	Grade III (21-30%)	LVH IV, coronary disease, or both	0	Abnormal, but no uremia
Class IV	——	K-W IV	Grade IV (over 30%)	——	Present	Uremia

unexplained variations. For example, Palmer and associates[14] reported a 22 per cent mortality in patients with mild hypertension compared to a 94 per cent mortality in patients with malignant hypertension during an 8-year period. Perera,[7] on the other hand, noted an average mortality of 17 per cent in patients with hypertension of all grades of severity after an average 12 years.

Since the beginning of the present study, a number of articles have appeared that clarify some of the factors influencing prognosis. Particularly to be noted are the publications of Griep and his associates,[15] Leishman,[16] Simpson and Gilchrist,[17] Bechgaard,[18] and Palmer and Muench.[19] No study reported to date, however, has completely filled the requirements for a prospective evaluation of consecutive cases of hypertension.

The present study was undertaken to obtain prospective data on the factors influencing mortality in a group of unselected consecutive hypertensive patients treated solely by conservative methods. Data on the prognosis in such cases should prove of value in evaluating the effect of therapeutic agents and procedures on the course of hypertension.

Selection of Subjects and Methods of Procedure

All cases of sustained hypertension (blood pressure greater than 150/90 mm. Hg on at least three occasions) were solicited from the general medical outpatient clinic for consultation and follow-up in the hypertension clinic. Each patient referred was registered consecutively and followed for at least 5 years or until death.

Soon after registration, pertinent data obtained from the history, physical examination, and laboratory studies in each case, including age, sex, race, obesity, family history of hypertension, duration of disease, and presence and degree of fundal, cardiac, cerebral, and renal involvement, were recorded on IBM punch cards. The degree of involvement was coded according to a grading system discussed below.

Grading of Degree of Involvement of Organ Systems at Registration

Blood Pressure

The initial blood pressure was classified arbitrarily as grade I (150-200/90-110), grade II (200-250/110-130), or grade III (over 250/130). The blood pressure recorded on the IBM card was the first reading taken in the hypertension clinic. In all cases it was taken without preliminary conversation after the patient had rested supine for 20 minutes in a quiet room. The ordinary blood pressure cuff, 13 cm. wide, was used routinely; for patients with unusually obese arms, however, leg cuffs were employed. Disappearance of sound was recorded as the diastolic pressure.

This blood pressure represents a resting outpatient reading by a uniform technic. It is a reading that can be obtained in a clinic or private office. This is not a "casual" or "basal" blood pressure reading as defined by Smirk,[20] Perera,[21] or Simpson and Gilchrist,[17] but is closer to the "near basal" recordings of Veale and his associates.[22]

Fundal Changes

The involvement of the ocular fundi, confirmed by an ophthalmologist, was classified from I to

Table 2

Original Case Material for Hypertension Follow-up Study

Total patients registered June 1946—June 1953			627
Patients lost before end of 5-year follow-up period			51
Number excluded from study			137
Secondary hypertension		47	
Coaretation	8		
Primary renal disease	37		
Pheochromocytoma	2		
Sympathectomy or adrenalectomy		27	
Treatment with ganglion-blocking drugs		47	
Age (over 69 years)		14	
Miscellaneous		2	
Total patients remaining for prognostic evaluation			439
Men	143		
Women	296		

IV according to Keith and Wagener's classification.[23]

Electrocardiographic Changes

Electrocardiographic patterns were classified as normal, borderline, nonspecific abnormality, coronary disease, or left ventricular hypertrophy.[24] Left ventricular hypertrophy was subdivided further: high voltage was classified as grade I, high voltage associated with relatively low T waves (less than 10 per cent of the R wave) as grade II, diphasic T waves with S-T changes as grade III, and clearly inverted T waves with or without voltage or conduction defects as grade IV.

Cardiac Size

The degree of cardiac enlargement as determined by x-ray examination was classified according to the Ungerleider and Gubner tables.[25] Grade I indicates 0 to 10 per cent enlargement; grade II, 11 to 20 per cent enlargement; grade III, 21 to 30 per cent enlargement; and grade IV, over 30 per cent enlargement.

Cardiac Status

Note was made whether patients had a clinically normal heart or whether they had signs and symptoms of congestive failure, or a history of angina pectoris or myocardial infarction.

Cerebral Status

The previous occurrence of transient pareses or cerebrovascular accidents was recorded as evidence of cerebral involvement. The presence of headache, dizziness, or unusual nervous tension was tabulated.

Renal Status

Renal function was graded as normal, impaired, or uremic; the presence of hematuria, pyuria, or bacteriuria was also noted.

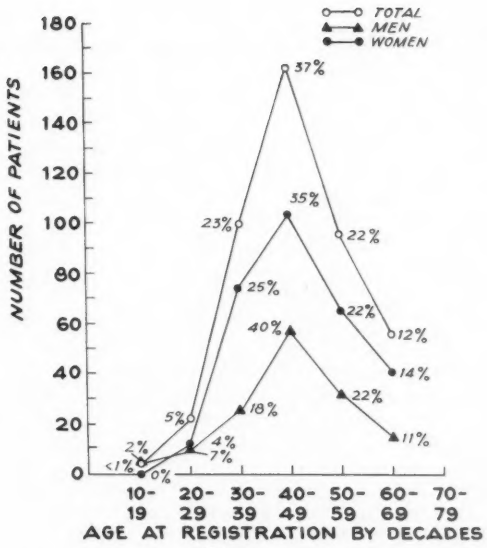

Figure 1

Age distribution at registration of patients in hypertension follow-up.

Treatment

After registration and evaluation of initial status, the patients were seen in the clinic at intervals of 1 week to several months, depending on the severity of the disease and their complaints. Therapy included mild sedation with phenobarbital, weight reduction when indicated, and several degrees of sodium restriction. Between 1950 and 1953, a few patients with accelerated hypertension were treated with ganglion-blocking drugs; these were later excluded from the study. By 1955 Rauwolfia alkaloids were being used in small doses, usually 0.25 mg. of reserpine as the maximum daily amount. Patients treated with reserpine were not excluded from the study, even if the therapy preceded the completion of the minimum 5-year follow-up period. The inclusion of these patients appears justified, since the low doses used did not lower the resting outpatient blood pressure readings; furthermore, any changes effected by the drugs would be in the direction of improving prognosis.

Duration of Follow-up

An intensive effort was made to keep in touch with all patients registered at the clinic. By the end of the study in June 1958, 92 per cent of the group had been followed until death or for at least 5 years. At this time, the duration of

Table 3

Grades of Initial Vascular Involvement and Severity of Hypertension in 439 Patients in Study Group

Vascular involvement	Total patients		Men		Women	
	No.	%	No.	%	No.	%
Blood pressure						
Grade I	192	44.0	61	42.5	131	44.0
Grade II	176	40.0	55	38.5	121	41.0
Grade III	71	16.0	27	19.0	44	15.0
Fundal classification						
K-W I	139	32.0	48	34.5	91	31.0
K-W II	217	50.5	57	41.0	160	55.0
K-W III	49	11.5	19	13.5	30	10.5
K-W IV	25	6.0	15	11.0	10	3.5
Size of heart (x-ray)						
Grade I	270	64.0	70	51.0	200	70.0
Grade II	101	24.0	42	30.0	59	21.0
Grade III	24	6.0	11	8.0	13	5.0
Grade IV	26	6.0	15	11.0	11	4.0
Electrocardiogram						
Normal	157	45.0	42	36.0	115	49.0
LVH I	43	12.0	11	9.5	32	13.5
LVH II	49	14.0	14	12.0	35	15.0
LVH III	34	10.0	13	11.5	21	9.0
LVH IV	68	19.0	36	31.0	32	13.5
Over-all severity						
Class I	81	18.5	25	17.0	56	19.0
Class II	176	40.0	45	32.0	131	45.0
Class III	106	24.0	40	28.0	66	22.0
Class IV	76	17.5	33	23.0	43	14.0

follow-up was noted on the patients' IBM cards. In the case of death, the date, cause, and autopsy information, when available, were added to the cards. Autopsy data were obtained from hospitals or coroners' files, and death certificates were requested from the Department of Public Health, State of California.

Method of Determining Results

At the end of this study, the material coded originally on the individual IBM cards was tabulated. The cards were sorted to determine the mortality in men and women by year and the cumulative mortality during the 5-year period on the basis of the items coded at the beginning of the study. Correlations were made among multiple factors. At this time it became apparent that certain of the coded items could not be evaluated, either because the number of patients was too small or because in retrospect the original basis for classification seemed not precise. For this reason, race, occupation, family history of hypertension, and duration of disease were excluded from the correlations.

An attempt was made to evaluate the over-all severity of hypertension at the time of registration as a factor in prognosis. The patients were grouped into four classes on the basis of increasingly severe grades of vascular involvement listed in table 1. The most advanced grade of vascular involvement in a patient, whether in a single or in multiple systems, was used as the index for classification.

Atherosclerosis as a prognostic factor, as distinguished from hypertension, required special attention. Since the presence and degree of atherosclerosis in the absence of complications are impossible to determine in vivo, we arbitrarily classified myocardial infarction, angina pectoris, cerebral thrombosis or hemorrhage, and transient paresis as manifestations of atherosclerotic processes. Cerebral hemorrhage may be caused by congenital vascular abnormalities as well as by atherosclerosis. Its inclusion, however, was considered justified on the grounds that cerebral hemorrhage and thromboses are often difficult to separate and that both may be associated with atherosclerosis.

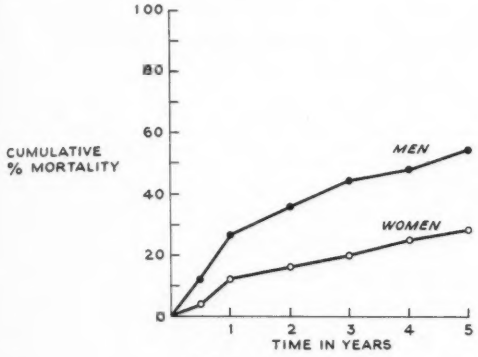

Figure 2

Relationship of mortality and sex.

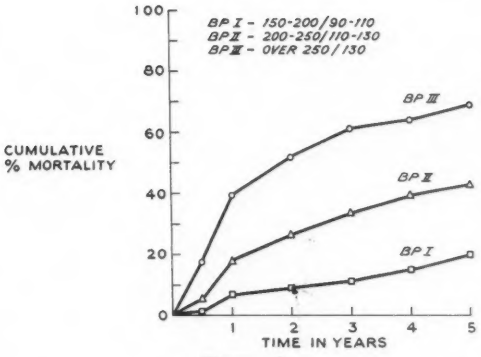

Figure 3

Relationship of mortality and initial blood pressure.

Results

Status at the Time of Registration

A total of 627 cases was registered in the hypertension clinic between June 1946 and June 1953, 137 of which were excluded at the time of compilation of the data (1958-1959) (table 2). The remaining 439 patients (143 men and 296 women) form the basis of this study. The age distribution of this group at the time of registration as well as of the men and women separately is shown in figure 1. For both men and women, the largest distribution of patients was in the fifth decade.

The distribution of the entire group among the four classes of severity, by use of the criteria for classification in table 2, and among all grades of vascular involvement, is as shown in table 3; while table 4 shows the age and sex distribution of the four classes of severity on initial examination. The incidence of atherosclerotic manifestations among the four classes as well as among men and women is outlined in table 5.

Mortality

At the end of the 5-year follow-up period, 161 of the 439 patients were dead. The influence of various factors observed on registration on the mortality is described below.

Relationship of Mortality and Sex

Seventy-eight (55 per cent) of the 143 men and 83 (28 per cent) of the 296 women in the group died during the 5-year period. The difference in mortality between the sexes is highly significant ($p < .001$). As shown by the curves graphed in figure 2, this difference was evident in the first year of the follow-up period and yearly thereafter. It

Table 4

Age, Sex, and Initial Severity of Hypertension in Study Group of 143 Men and 296 Women

	Severity of hypertension											
	Class I			Class II			Class III			Class IV		
Age	Total	Men	Women	Total	Men	Women	Total	Men	Women	Total	Men	Women
Under 20	3	3	0	0	0	0	0	0	0	0	0	0
20-29	5	3	2	11	5	6	6	2	4	0	0	0
30-39	19	7	12	46	9	37	21	8	13	14	2	12
40-49	28	9	19	67	19	48	36	15	21	31	15	16
50-59	18	3	15	34	8	26	26	9	17	18	11	7
60-69	8	0	8	18	4	14	17	6	11	13	5	8
Total	81	25	56	176	45	131	106	40	66	76	33	43

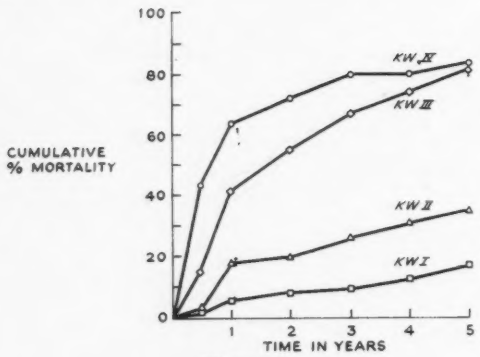

Figure 4

Relationship of mortality and initial fundal classification.

is apparent from table 6 that a higher relative percentage of the men were included in classes III and IV severity, while a higher proportion of the women were included in classes I and II severity. In each of the four classes of severity, the men had a higher mortality rate than the women. Not only did the men have a higher degree of severity initially than the women but even at equivalent grades of severity the men had a higher mortality. This difference in mortality was not due to a difference in age between the two groups, since the average age of men and of women in each class of severity was not significantly* different.

Relationship of Mortality and Initial Blood Pressure

Figure 3 shows the yearly cumulative per cent mortality in patients with three grades of blood pressure on initial examination. The difference in 5-year mortality between successive degrees of elevation is highly significant ($p < .001$), and the difference is obvious at each year of observation. Increasing age is not a significant factor in the increasing mortality within grade of blood pressure elevation by the χ^2 test. However, the dependence of mortality on sex for each grade of blood pressure elevation is significant, and with each grade of hypertension a significantly larger proportion of the men than of the women died.

*Whenever the term "significant" is used in this paper, it refers to "statistically significant," with a p value less than, or equal to, 0.05.

Table 5

Prevalence of Atherosclerotic Manifestations in Men and Women in Four Classifications of Hypertension

Severity of hypertension	Atherosclerotic manifestations					
	Present			Absent		
	Total	Men	Women	Total	Men	Women
Class I	12	3	9	69	22	47
Class II	38	9	29	138	36	102
Class III	45	16	29	61	24	37
Class IV	17	9	8	59	24	35
Total	112	37	75	327	106	221

Relationship of Fundal Classification to Mortality

Figure 4 illustrates the yearly mortality with four grades of fundal involvement. The differences in 5-year mortality between successive degrees of severity is highly significant ($p<.001$). There is no significant correlation of age with mortality at any level of fundal classification. With Keith-Wagener grade I and II changes, survival is significantly higher among women than among men. With grade III and IV Keith-Wagener changes, no significant difference between the sexes appears.

Relationship of Heart Size and Mortality

Figure 5 illustrates the yearly mortality with four grades of cardiac enlargement determined by radiography of the chest by means of the Ungerleider tables. The difference in mortality between successive degrees of enlargement is highly significant ($p < .001$), and the difference is noted at each year of observation. No significant correlation was found between mortality and age. The mortality was significantly greater in men than in women only in grade I enlargement; no significant dependence of mortality and sex was found for the three higher degrees of enlargement. It is of note that none of the 26 patients with greater than 30 per cent cardiac enlargement survived 5 years.

Relationship of Left Ventricular Hypertrophy by Electrocardiogram and Mortality

The yearly cumulative per cent mortality in patients with normal electrocardiogram and with four grades of left ventricular

hypertrophy is graphed in figure 6. A significant difference in mortality was found between the normal electrocardiogram and grades I and II left ventricular hypertrophy combined and grades III and IV left ventricular hypertrophy combined. No dependence of mortality on age was found, and the dependence of sex was significant only for milder grades of left ventricular hypertrophy (grades I, II, and III combined), not for the normal electrocardiogram or grade IV left ventricular hypertrophy.

Relationship of Over-all Hypertensive Severity and Mortality

The 5-year mortality of patients in the four classes of hypertensive severity is graphed in figure 7. The increasing mortality with increasing severity is apparent. The relative prognostic significance of the individual criteria for classification among the four classes of severity was determined separately. In patients who had grade II blood pressure but were grade I in all other categories, the 5-year mortality was 11.5 per cent; in those with Keith-Wagener grade II changes and all else grade I, the 5-year mortality was 11.9 per cent; in those with electrocardiogram grade II changes and all else grade I, the 5-year mortality was 10.0 per cent. This indicates that the criteria making up class

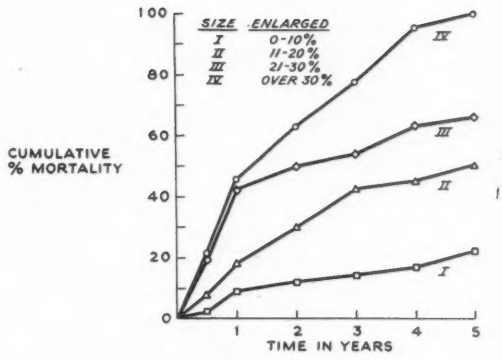

Figure 5

Relationship of mortality and initial heart size. (Ungerleider-Gubner tables)

II hypertensive severity were approximately equal in importance. In class III hypertension, however, the presence of Keith-Wagener grade III fundal changes as the only class III criterion caused a 66.6 per cent mortality while blood pressure grade III had a 27.8 mortality, heart size grade III had a 33.3 per cent mortality, and left ventricular hypertrophy grade IV had a 42.9 per cent mortality. In class IV severity, patients who were classified class IV on the basis of congestive heart failure alone had a 57 per cent mortality, while those classified on the basis of grade IV fundal changes or grade IV heart size

Table 6

Initial Severity of Hypertension in Men and Women as a Factor in Prognosis

Severity of hypertension	Men			Women		
	Total	Alive	Dead	Total	Alive	Dead
Class I	25	21	4 (16%)	56	51	5 (9%)
Class II	45	27	18 (40%)	131	113	18 (15%)
Class III	40	14	26 (65%)	66	40	26 (39%)
Class IV	33	3	30 (91%)	43	9	34 (79%)

Table 7

Cause of Death in Relation to Initial Severity of Hypertension*

Severity of hypertension	Total no. deaths	"Hypertensive" causes			Coronary thrombosis	Cerebrovascular accident	Dissecting aneurysm	Noncardiovascular causes
		Cardiac failure	Uremia	Malignant hypertension				
Classes I & II	32	2	0	1	8	11	0	10
Classes III & IV	121	19	9	17	25	41	3	7

*In an additional eight patients, cause of death was unknown.

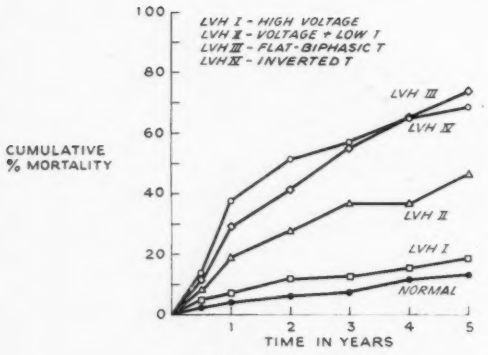

Figure 6

Relationship of mortality and initial degree of left ventricular hypertrophy (ECG).

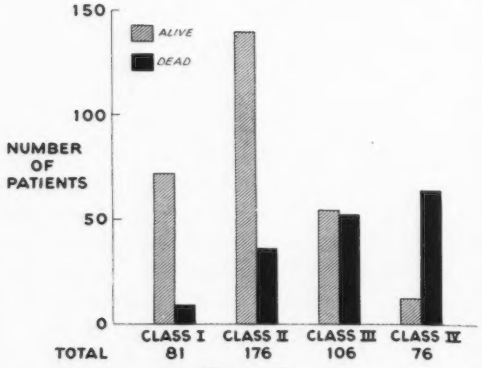

Figure 7

Mortality according to severity of disease (class I to IV).

had a 73.4 per cent and 100 per cent mortality, respectively. In evaluating the relatively low mortality of congestive failure as a criterion, it was noted that all patients with congestive heart failure and other associated class IV criteria were dead; two thirds of those with congestive failure and associated class III criteria, and one half of those with congestive heart failure and associated class I or II criteria were dead. In reviewing the charts in this last group, the diagnosis of congestive heart failure was based on hepatomegaly and the presence of a few rales. Since interpretation of early congestive failure in patients with a regular rhythm is often difficult, it is possible that these patients had either minimal left ventricular failure or that the physical findings were due to another cause.

Relationship of Atherosclerotic Manifestations and Mortality

The mortality of patients classified in the four classes of hypertensive severity with and without atherosclerotic manifestations is illustrated in figure 8. The presence of atherosclerosis significantly increased the mortality of patients with classes I and II hypertension combined. The mortality of class I patients without atherosclerosis was 9 per cent, while those with atherosclerosis had a 25 per cent mortality. The difference in mortality in classes III and IV combined between those patients with and those without atherosclerotic manifestations is not significant ($p > .05$). The presence of atherosclerotic manifestations as a possible cause of the difference between the mortality of men and women was investigated. Thirty-seven of the 143 men had atherosclerotic manifestations; 25 (57 per cent) were dead within 5 years. Seventy-five of the 296 women had atherosclerotic complications; 29 (36 per cent) were dead within 5 years. Atherosclerotic manifestations occurred in all four classes of severity; 74 per cent occurred in classes II and III severity. The age of patients with atherosclerotic manifestations in both sexes was higher than the age of patients without atherosclerotic manifestations.

Cause of Death

The cause of death was established in 151 of the 159 patients who died. A comparison of the relative frequency of the main causes of death in men and women is illustrated in figure 9. Only 17 patients died of noncardiovascular causes. The incidence of malignant hypertension was high in this series and would have been higher if all patients with Keith-Wagener grade IV changes treated with ganglion-blocking agents had not been excluded from the original group of patients. The higher incidence of coronary deaths and malignant hypertension in men and the higher incidence of cerebrovascular accidents in

Table 8

Initial Blood Pressure as a Factor in Prognosis: Alone and in Correlation with Other Vascular Abnormalities

	Initial blood pressure								
	Grade I			Grade II			Grade III		
	Total	Alive	Dead	Total	Alive	Dead	Total	Alive	Dead
Blood pressure alone	190	152	38	176	102	74	72	23	49
Blood pressure associated with:									
Fundal classification									
K-W I	98	85	13	69	28	41	4	2	2
K-W II	79	61	18	71	63	8	34	17	17
K-W III	6	4	2	23	6	17	20	1	19
K-W IV	3	1	2	10	2	8	12	2	10
Size of heart (x-ray)									
Grade I	143	121	22	107	80	27	20	11	9
Grade II	31	26	5	41	15	26	28	10	18
Grade III	6	2	4	12	5	7	6	1	5
Grade IV	4	0	4	9	0	9	13	0	13
Electrocardiogram									
Normal	94	86	8	53	45	8	9	5	4
Borderline	28	25	3	23	13	10	3	1	2
LVH I	22	20	2	19	14	5	4	3	1
LVH II	13	10	3	23	10	13	13	6	7
LVH III	8	4	4	16	4	12	10	1	9
Cardiac status									
Normal	100	88	12	62	45	17	16	8	8
Signs of failure	13	7	6	16	3	13	14	0	14
Angina	18	10	8	20	12	8	3	0	3
Myocardial infarct	3	0	3	2	1	1	0	0	0
Renal function									
Normal	161	136	25	131	88	43	39	18	21
Impaired	15	6	9	32	9	23	28	3	25
Cerebral manifestations									
Headache	67	57	10	106	65	41	38	13	25
Dizziness	42	34	8	52	28	24	21	8	13
Transient paresis	9	7	2	17	6	11	8	4	4
Cardiovascular accident	16	9	7	25	12	13	9	3	6

women are to be noted. The average age at death was 51 years for the men and 50 years for the women, whereas the average age at registration was 45 and 47 years respectively for men and women.

Table 7 compares the causes of death in classes I and II combined (mild to moderate cases) with classes III and IV combined (more severe and accelerated cases). Since much of this information is derived from death certificates and reports from coroners and private physicians, there is often no clear differentiation between congestive failure on the basis of left ventricular failure secondary to long-standing hypertension and congestive failure on the basis of multiple or extensive myocardial infarctions. It appears that the majority of the deaths in classes I and II hypertensive severity were "atherosclerotic" or noncardiovascular rather than purely hypertensive, whereas in classes III and IV the deaths were both atherosclerotic and hypertensive.

There were unexpectedly prolonged survivals in the more severe classes of severity, just as there were unexpected early deaths in the mild classes of severity. Thus occasional patients with advanced disease and involve-

Table 9

Initial Fundal Classification as a Factor in Prognosis: Alone and in Correlation with Other Vascular Abnormalities

	Initial fundal classification											
	Grade I			Grade II			Grade III			Grade IV		
	Total	Alive	Dead	Total	Alive	Dead	Total	Alive	Dead	Total	Alive	Dead
Fundal changes alone	139	116	23	217	141	76	49	11	38	25	5	20
Fundal changes associated with:												
Blood pressure												
Grade I	98	85	13	79	61	18	6	4	2	3	1	2
Grade II	36	28	8	104	63	41	23	6	17	10	2	8
Grade III	4	2	2	34	17	17	20	1	19	12	2	10
Size of heart (x-ray)												
Grade I	117	102	15	127	95	32	15	8	7	6	3	3
Grade II	14	10	4	60	37	23	16	2	14	10	2	8
Grade III	2	2	0	13	5	8	5	1	4	3	0	3
Grade IV	2	0	2	9	0	9	10	0	10	5	0	5
Electrocardiogram												
Normal	78	71	7	70	61	9	6	3	3	2	1	1
Borderline	23	19	4	28	19	9	2	0	2	1	1	0
LVH I	18	16	2	23	17	5	2	0	2	1	1	0
LVH II	8	4	4	29	20	9	7	1	6	5	1	4
LVH III	6	3	3	16	4	12	7	1	6	3	0	3
LVH IV	5	4	1	33	13	20	17	3	14	11	1	10
Coronary disease	7	4	3	17	7	10	8	1	7	3	0	3
Cardiac status												
Normal	86	75	11	74	59	15	11	3	8	5	2	3
Signs of failure	7	3	4	19	6	13	9	1	8	7	0	7
Angina	10	8	2	22	13	9	5	1	4	3	0	3
Myocardial infarct	1	0	1	4	1	3	0	0	0	0	0	0
Renal function												
Normal	121	106	15	181	129	52	21	5	16	6	3	3
Impaired	7	4	3	25	6	19	22	5	17	19	2	17
Cerebral manifestations												
Headache	63	57	6	103	67	36	29	6	23	16	5	11
Dizziness	31	26	5	60	40	20	15	1	14	7	3	4
Transient pareses	7	4	3	18	12	6	6	0	6	2	1	1
Cardiovascular accident	0	0	0	0	0	0	0	0	0	0	0	0

ment of multiple organs and systems survived for 10 years or more, while others who appeared to have a very favorable prognosis died unexpectedly early in the course of follow-up. Some of the patients with prolonged survivals who were classified in classes III and IV severity were placed in these categories because of previous coronary disease or renal impairment, which remained relatively stationary for many years. Occasionally a patient was placed in a more severe class because of an initially high blood pressure that could have been due to emotional causes not recognized at the time of initial examination.

Correlation of Mortality and Involvement in Multiple Systems

Tables 8 through 11 tabulate the vascular complications associated with each grade of severity of blood pressure, fundal classification, cardiac size, and electrocardiographic abnormality. The 5-year mortality for multiple pairs of associated conditions is recorded. It is apparent that patients with minimal involvement in one organ system tended to have only grade I or II involvement

Table 10

Initial Size of Heart as a Factor in Prognosis: Alone and in Correlation with Other Vascular Abnormalities

	Initial size of heart											
	Grade I			Grade II			Grade III			Grade IV		
	Total	Alive	Dead	Total	Alive	Dead	Total	Alive	Dead	Total	Alive	Dead
Size of heart alone	270	212	58	101	51	50	24	8	16	26	0	26
Size of heart associated with:												
Blood pressure												
Grade I	143	121	22	31	26	5	6	2	4	4	0	4
Grade II	107	80	27	42	15	27	12	5	7	9	0	9
Grade III	20	11	9	28	10	18	6	1	5	13	0	13
Fundal classification												
K-W I	117	102	15	14	10	4	2	2	0	2	0	2
K-W II	127	95	32	60	37	23	13	5	8	9	0	9
K-W III	15	8	7	16	2	14	5	1	4	10	0	10
K-W IV	6	3	3	10	2	8	3	0	3	5	0	5
Electrocardiogram												
Normal	128	115	13	21	15	6	1	1	0	0	0	0
Borderline	45	35	10	8	5	3	0	0	0	0	0	0
LVH I	33	28	8	11	8	3	0	0	0	0	0	0
LVH II	26	17	9	15	6	9	8	4	4	1	0	1
LVH III	13	7	6	13	1	12	1	1	0	4	0	4
LVH IV	13	6	7	25	12	13	14	3	11	14	0	14
Coronary disease	15	7	8	14	5	9	4	0	4	2	0	2
Cardiac status												
Normal	150	125	25	19	12	7	3	0	3	0	0	0
Signs of failure	7	3	4	15	5	10	6	2	4	14	0	14
Angina	17	13	4	11	7	4	5	1	4	6	0	6
Myocardial infarct	1	0	1	1	0	1	1	0	1	0	0	0
Renal function												
Normal	227	189	38	70	41	29	14	6	8	7	0	7
Impaired	25	10	15	26	7	19	8	1	7	14	0	14
Cerebral manifestations												
Headache	134	107	27	50	22	28	12	4	8	8	0	8
Dizziness	62	47	15	32	19	13	9	2	7	4	0	4
Transient pareses	19	12	7	13	5	8	1	0	1	1	0	1
Cardiovascular accident	30	18	12	12	4	8	5	1	4	1	0	1

in other systems. Of 270 patients with grade I heart size (0 to 10 per cent enlargement), 206 had a normal electrocardiogram or minimal left ventricular hypertrophy; 244 had grade I or II Keith-Wagener changes in the fundi; and 143 had a blood pressure grade I. In contrast, the patients with severe involvement in one organ system generally had advanced grades of involvement in other organs. Of 26 patients with grade IV heart size (over 30 per cent enlargement), 20 had advanced left ventricular hypertrophy, 15 had grade III or IV Keith-Wagener changes in the fundi, and 15 had a blood pressure exceeding 250/130, while 14 had impaired renal function or signs of congestive heart failure. Those patients with mild involvement in one or more organ systems had a relatively low 5-year mortality, while patients with moderate or marked involvement of one organ system had a high mortality, which was even higher when multiple systems showed evidence of advanced disease.

At this point it is of interest to note that of 439 patients in the entire group, only 57 had a blood pressure in the range of 150-200/

Table 11

Initial Electrocardiographic Status as a Factor in Prognosis: Alone and in Correlation with Other Vascular Abnormalities

	Initial electrocardiographic status														
	Normal			LVH I			LVH II			LVH III			LVH IV		
	Total	Alive	Dead	Total	Alive	Dead	Total	Alive	Dead	Total	Alive	Dead	Total	Alive	Dead
Ecg. status alone	154	135	19	43	35	8	49	26	23	34	9	25	68	21	47
Ecg. status associated with:															
Blood pressure															
Grade I	94	86	8	22	20	2	13	10	3	8	4	4	11	3	8
Grade II	51	43	8	17	12	5	23	10	13	16	4	12	31	13	18
Grade III	9	5	4	4	3	1	13	6	7	10	1	9	26	5	21
Fundal classification															
K-W I	74	68	6	17	15	2	8	4	4	6	3	3	5	4	1
K-W II	71	62	9	20	16	4	29	20	9	16	4	12	33	13	20
K-W III	5	2	3	2	0	2	7	1	6	7	2	5	17	3	14
K-W IV	2	1	1	1	1	0	5	1	4	3	0	3	11	1	10
Size of heart (x-ray)															
Grade I	127	114	13	31	26	5	26	17	9	13	7	6	13	6	7
Grade II	20	14	6	10	8	2	15	6	9	13	1	12	25	12	13
Grade III	1	1	0	0	0	0	6	3	3	2	1	1	14	3	11
Grade IV	0	0	0	0	0	0	1	0	1	4	0	4	14	0	14
Cardiac status															
Normal	83	75	8	23	20	3	16	11	5	9	5	4	5	1	4
Signs of failure	1	1	0	4	2	2	5	2	3	6	1	5	17	1	16
Angina	10	10	0	4	2	2	2	1	1	4	1	3	11	4	7
Myocardial infarct	1	1	0	0	0	0	0	0	0	0	0	0	0	0	0
Renal function															
Normal	134	116	17	36	31	5	35	23	12	20	5	15	38	16	22
Impaired	3	2	1	4	2	2	9	1	8	12	4	8	25	5	20
Cerebral manifestations															
Headache	63	54	9	17	14	3	27	17	10	17	3	14	34	12	22
Dizziness	35	29	6	12	10	2	14	9	5	6	0	6	22	8	14
Transient pareses	9	6	3	5	3	2	9	3	6	2	0	2	6	3	3
Cardiovascular accident	14	9	5	5	4	1	10	3	7	4	2	2	9	4	5

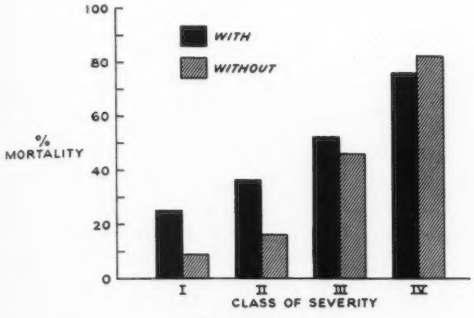

Figure 8

Mortality of patients with and without atherosclerotic complications.

90-100 (grade I) with no other abnormality. Of these, 51 were alive and six were dead within the 5-year follow-up period. Only 20 patients had a blood pressure of 200-250/110-130 (grade II) with no other abnormality. Nineteen of these survived the 5-year period. There were no patients with a blood pressure over 250/130 with no other organ involvement.

Symptoms

The correlations of tables 12, 13, and 14 clarify the apparently high mortality in patients with symptoms such as headaches, dizziness, and nervous tension. The mortality of all patients coded "headache," disregarding all other variables, was 36 per cent. However, when headache was associated with grade I blood pressure elevation, the mortality was 15 per cent; with grade II blood pressure elevation it was 39 per cent; and with grade III blood pressure elevation it was 80 per cent. This suggests that the mortality was a factor of the associated vascular involvement rather than of the headache alone. Similar observations were recorded with dizziness and with nervous tension alone and in association with progressive grades of vascular abnormality.

Obesity

Table 15 compares the mortality among clinically obese and nonobese patients classified according to age and degree of vascular involvement. It is apparent that there were approximately as many patients with obesity as nonobese patients in each classification. However, the over-all mortality among the obese patients was significantly lower than among the nonobese patients. For instance, with grade I fundal changes, 12 per cent of the obese patients were dead while 24 per cent of the nonobese patients were dead. Likewise, with grade III fundal changes, 56 per cent of the obese patients were dead and 94 of the nonobese patients were dead.

Table 12

Headache as a Factor in Prognosis: Alone and in Correlation with Grades of Vascular Abnormalities

	Total no. of patients	Alive No.	Alive %	Dead No.	Dead %
Headache alone	212	136	64	76	36
Headache associated with:					
Blood pressure					
Grade I	67	57	85	10	15
Grade II	106	65	61	41	39
Grade III	38	13	20	25	80
Fundal Classification					
K-W I	63	57	90	6	10
K-W II	103	67	65	36	35
K-W III	29	6	21	23	79
K-W IV	16	5	31	11	69
Size of heart					
Grade I	134	107	80	27	20
Grade II	50	22	44	28	56
Grade III	12	4	33	8	67
Grade IV	8	0	0	8	100
Electrocardiogram					
LVH I	17	14	82	3	18
LVH II	27	17	63	10	37
LVH III	17	3	18	14	82
LVH IV	34	12	35	22	65

Discussion

The higher mortality in men than in women was evident in all classes of severity and at all ages. On the whole, the men registered at a more advanced stage in their disease, but even at comparable degrees of hypertensive severity, proportionately more men died than women. This may be due in part to the higher incidence of coronary atherosclerosis in men. It has been observed before that the incidence of malignant hypertension is higher in men than in women; this also contributes to the higher mortality.[26] The

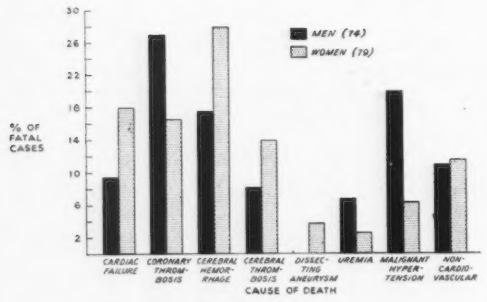

Figure 9

Comparison of cause of death in men and women.

average age at death of men and women, 51 years and 50 years respectively, is not significantly different and compares with the figure of 52 years Perera[7] gives for men and women combined.

The results show that in patients with hypertension the death rate increases with progressive degrees of impairment of the major organ systems. Even in patients with mild hypertension, i.e., minimal elevation of blood pressure and no cardiac involvement, the mortality is higher than in the population at large. The mortality would probably be lower in an asymptomatic population in whom the hypertension was discovered by a routine examination rather than in an outpatient population as represented in our series. Our figures agree closely with actuarial figures on the rate of mortality in men and women with average normal blood pressures and those with above average elevation of blood pressure.[27] For instance, the average blood pressure in men aged 45 years is 126/78 mm. Hg; the mortality is increased 300 per cent if this pressure is elevated to 152/95 (grade I blood pressure by our criteria). In our patients with class I hypertension but no atherosclerotic manifestations, we found a 9 per cent mortality, roughly three times the normal expected at age 45. The increased mortality is evident after 1 year of follow-up and continues yearly thereafter. Perera[28] concluded that by the time an average hypertensive patient develops complications he has already survived three fourths of his hypertensive life span. It appears

Table 13

Dizziness as a Factor in Prognosis: Alone and in Correlation with Grades of Vascular Abnormalities

	Total no. of patients	Alive No.	Alive %	Dead No.	Dead %
Dizziness alone	116	71	61	45	39
Dizziness associated with:					
Blood pressure					
Grade I	42	34	81	8	19
Grade II	52	28	54	24	46
Grade III	21	8	35	13	65
Fundal classification					
K-W I	33	26	79	7	21
K-W II	60	40	67	20	33
K-W III	13	1	8	12	92
K-W IV	5	3	60	2	40
Size of heart					
Grade I	62	47	76	15	24
Grade II	32	19	59	13	41
Grade III	9	2	22	7	78
Grade IV	4	0	0	4	100
Electrocardiogram					
LVH I	12	10	83	2	17
LVH II	14	9	64	5	36
LVH III	6	0	0	6	100
LVH IV	22	8	36	14	64

that even minimal electrocardiographic and radiologic changes of hypertrophy are generaly indicative of sequelae that herald a premature death, unless the trend can be reversed by modern drugs.

The variability of blood pressure levels in hypertensive patients makes it mandatory to define the circumstances under which the blood pressure is taken (basal, near-basal, resting, and casual) in order to evaluate its significance in prognosis.[17, 29] The presence of acutely disturbing emotional factors, which raise the blood pressure to unusual levels, will introduce an error into the predictions (this probably explains the occasional high readings in patients without vascular complications), but it is interesting that blood pressure grade III was never an isolated finding. The presence of undetected atherosclerosis in otherwise grade I patients will similarly affect the prognosis adversely.

The progressive increase in mortality with increasing grades of elevated blood pressure (figure 3) is noteworthy in view of repeated reports in the literature stressing the unrelia-

Table 14

"Nervous Tension" as a Factor in Prognosis: Alone and in Correlation with Grades of Vascular Abnormalities

	Total no. of patients	Alive No.	Alive %	Dead No.	Dead %
"Nervous tension" alone	230	155	67	75	33
"Nervous tension" associated with:					
Blood pressure					
Grade I	93	78	84	15	16
Grade II	103	70	68	33	32
Grade III	34	7	20	27	80
Fundal classification					
K-W I	75	62	83	13	17
K-W II	117	82	70	35	30
K-W III	21	4	19	17	81
K-W IV	14	4	28	10	72
Size of heart					
Grade I	153	125	82	28	18
Grade II	50	25	50	25	50
Grade III	12	4	53	8	67
Grade IV	9	0	0	9	100
Electrocardiogram					
LVH I	23	18	78	5	22
LVH II	22	14	64	8	36
LVH III	9	5	56	4	44
LVH IV	34	11	37	23	63

bility of single casual blood pressures in prognosis. It is obvious that the blood pressure, as we obtained it, is not "casual" but closer to the "near-basal"[22] in the continuum of daily blood pressures. In our patients, the blood pressure level used for tabulation was the third or fourth casual reading and was taken after the patient had rested 20 minutes and before any conversation or questions. Apparently a blood pressure taken under these circumstances can be used for prognostic purposes.

The prevalence of vascular complications was also much higher with increasing grades of blood pressure. For example, table 8 shows that of 190 patients with blood pressure grade I, only nine had grade III or IV Keith-Wagener fundal changes; only 10 had left ventricular hypertrophy; only 10 had over 20 per cent cardiac enlargement. Of 72 patients with blood pressure grade III, 29 had grade III or IV Keith-Wagener fundal changes; 21 had grade IV left ventricular hypertrophy, and 18 had more than 20 per cent cardiac enlargement.

Table 15

Comparison of Age, Symptoms, Vascular Involvement and Mortality in 199 Obese and 240 Nonobese Hypertensive Patients

	Total no. patients	Obese Total	Obese % Dead	Nonobese Total	Nonobese % Dead
Age (years)					
10-19	3	0	0	3	0
20-29	22	5	0	17	15
30-39	100	53	23	47	36
40-49	162	72	28	90	43
50-59	96	42	28	54	58
60-69	56	27	48	29	48
Blood pressure					
Grade I	192	92	12	100	27
Grade II	176	71	20	105	48
Grade III	71	36	61	35	77
Fundal classification					
K-W I	139	90	12	49	24
K-W II	217	77	31	140	37
K-W III	49	20	80	29	76
K-W IV	25	9	56	16	94
Size of heart (x-ray)					
Grade I	270	128	14	142	30
Grade II	101	51	47	50	52
Grade III	24	8	50	16	75
Grade IV	26	10	100	16	100
Electrocardiogram					
Normal	157	69	1	88	15
LVH I	43	18	17	25	20
LVH II	49	25	28	24	67
LVH III	34	15	67	19	79
LVH IV	68	34	62	34	77
Atherosclerotic manifestations					
Present	54	18	36	36	58
Symptoms					
Headache	212	95	24	117	45
Dizziness	116	59	22	57	56
Nervous tension	230	103	27	127	37

Symptoms are often misleading in hypertensive patients, as has been discussed by Pickering,[30] Atchley,[31] and Fishberg.[32] This does not mean that dyspnea on exertion in a patient with congestive heart failure is meaningless, that dizziness associated with a cerebrovascular accident is to be ignored, or that severe headache in a patient with malignant hypertension is unimportant. But the symptoms of dizziness and headaches are not associated with increased mortality un-

less they are associated with objective evidence of vascular disease. The apparently better prognosis in obese patients remains unexplained but has been noted before by Frant and Groen.[33]

The increasingly mortality with progressive degrees and multiplicity of complications is clearly shown. By use of the χ^2 test it is apparent that progressive mortality with progressive vascular impairment is evident at each decade and that progressive age is not a significant factor within any grade.

The role of atherosclerosis in hypertension is difficult to evaluate. It may be an independently associated factor increasing mortality or it may appear or be accelerated secondary to long-standing hypertension. The group of patients with grade II Keith-Wagener fundal changes (representing arteriolar disease) did not have a significantly high incidence of angina pectoris, infarction, or cerebrovascular accidents, but did have a 35 per cent mortality. On the other hand, the group of patients with impaired renal function, presumably also due to arteriolar disease, since all known cases of primary renal disease were excluded from this study, had a 76 per cent mortality. The causes of death in the patients with mild or moderately severe hypertension were mainly coronary disease and cerebrovascular disease, which are probably largely manifestations of atherosclerosis. It will be of great importance to determine whether adequate blood pressure lowering in this group of mild and moderately severe hypertensives will significantly lower the mortality and decelerate the atherosclerotic process. Well-controlled studies will have to be done to test the effectiveness of modern drugs for this purpose.

Summary

Four hundred thirty-nine consecutive patients (143 men and 296 women) with essential hypertension were followed on conservative therapy for a minimum of 5 years or until death. The initial blood pressure taken by a standard method and the presence and degree of vascular involvement at the time of registration were recorded on all patients. On the basis of these observations, each patient was classified in one of four classes of over-all hypertensive severity.

At the end of the 5-year follow-up period, 161 patients were dead, 78 men and 83 women. The higher mortality among men was significant and was apparent after the first year of follow-up. A progressive rise in 5-year mortality was observed with increasing degrees of initial blood pressure elevation, fundal involvement, cardiac size by radiogram, and electrocardiographic evidence of left ventricular hypertrophy, as well as with progressively higher classification of over-all hypertensive severity. Patients with mild hypertension and minimal cardiovascular impairment (class I) had an 11 per cent 5-year mortality, while patients with malignant hypertension, renal failure, or congestive heart failure (class IV) had an 84 per cent 5-year mortality. Early deaths in patients with mild hypertension were found to be largely due to atherosclerotic complications or noncardiovascular causes. Possible explanations for long survivals in patients with advanced vascular involvement on initial examination are discussed. The increased mortality of men over women was attributed in part to greater severity of disease on initial registration and in part to a higher incidence of coronary atherosclerosis. The mortality in patients with headache, dizziness, and nervous tension was found to be a factor of the associated vascular complication rather than of the symptoms alone. Patients with clinical obesity were found to have a lower over-all mortality than patients who were not obese. The prognostic value of a standardized initial blood pressure measurement is stressed and is discussed in the light of previous work by Perera, Smirk, and Gilchrist. The prognostic data were presented as a framework against which the long-term treatment of mild and moderate hypertension can be tested.

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Twenty-Year Studies with the Ballistocardiograph

The Relation between the Amplitude of the First Record of "Healthy" Adults and Eventual Mortality and Morbidity from Heart Disease

By ISAAC STARR, M.D., AND FRANCIS C. WOOD, M.D.

THE LONG-TERM FOLLOW-UP of persons in whom one is interested, while always difficult to carry out, provides information of a type not duplicated by any other method of clinical investigation. This presentation relates the amplitude of ballistocardiograms to what we have called the physiologic age of the heart, and we have studied the relationship between such estimates of cardiac age, made about 20 years ago, and the after-histories of the subjects up to the present time, making use of the ordinary clinical criteria to judge the presence or absence of heart disease.

The large series of persons studied on our ballistocardiographs since our first instrument was constructed in 1936 can be divided into two main groups: *patients* attending the hospital because they were ill, and *healthy persons* who came to be tested at our request, chiefly to provide us with normal standards.[1, 2] This paper is concerned solely with the group who were healthy when first tested. Our long-term studies on the patients will be reported later.

Each healthy subject entered the study when his first ballistocardiogram was taken; this was in 1936 for a few, in 1937, 1938, and 1939 for the majority. A few others, chiefly medical students, entered the series from 1940 to 1943. The study was closed in 1959. The mean duration of the follow-up period is 20.5 years, the median is 21 years, and the range is from 23 to 17 years.

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Work on the normal standards had hardly been completed when the onset of war disrupted our plans and research activities related to immediate needs took precedence over all others. That something of interest was happening in the "normal standard" group became apparent after the war was over, so the data were studied and the first report followed.[3] In a second study[4] 80 persons were brought back for retesting with the ballistocardiograph, approximately 10 years after the first test. Preliminary reports of our recent experience have also been made.[5, 6]

The present study is based not only on the further after-histories of those who were studied 10 years ago, but also on the after-histories of many others not included in the previous reports. In this study we aimed at securing data from 200 healthy persons who could be followed for a long period of time after their first ballistocardiograms, and we slightly exceeded our aim; the number finally attained was 211. We would have liked to keep the sexes even, but we found it was much easier to secure men, mostly doctors and medical students who worked in the hospital, than women; and in the completed series, the men outnumber the women by a ratio of about 5 to 1.

During the long studies, our series divided itself into two groups, those who remained in or near Philadelphia and whom we continued to see almost daily, and those who moved away with whom we maintained contact by mail and by seeing them occasionally.

This communication is concerned with findings related to groups of our subjects. Discussion of the many interesting things that happened to individuals during the 20-year period will be reserved for later communications.

Methods and Sources of Information

The Group Studied

All our subjects belonged to the white race. Their ages, when the first ballistocardiogram was taken, ranged from 22 to 85 years. The series consisted of 174 men and 37 women. At the time of the first test, 112 were doctors, of either medicine or philosophy, and 64 were medical students. The others were drawn from established employees of the medical school or hospital and from the friends and family of the first author.

Ballistocardiograms

The original ballistocardiograms were all taken on our first high-frequency table,[7] the subjects being in the horizontal position with their heels in firm contact with the footboard. All these records were taken after a rest period of at least 15 minutes lying on the apparatus. Blood pressure was taken during this rest period. No record was taken less than 2 hours after a meal.

The follow-up ballistocardiograms were taken by the same technic on the same original instrument. In addition records were secured on both modern high-frequency and ultra-low frequency instruments.

Other Information

With those that remained in or near Philadelphia, our contact could hardly have been bettered. In this group are the 65 surviving men and 23 surviving women who have recently been given a complete cardiovascular study, the majority in Dr. Wood's office, a few in the hospital because they were ill. Also in this group can be placed the 30 men and four women who died during the period of observation after a careful study either in the University Hospital or in some other hospital in whose staff we have confidence. Therefore, this group, which totaled 122 persons, will be called the "maximum-contact" group. In these persons our opportunities for observing the development of disease could hardly have been bettered.

Our contact with the rest of our subjects has also been close, although we have not had the opportunity of making a complete cardiovascular study recently, and have had to rely for our recent information on occasional interviews and on a questionnaire sent by mail. All the men of this "lesser-contact group" were doctors well acquainted with the nature of the study and its importance. Our letter inquiring about their present health was answered by all but three persons; the possibility that these three might have failed to respond because they were dead was rendered unlikely by finding that they were still on the active list in the files of our alumni association, and listed as in practice by the medical directory.

Considering both groups together, the results of thorough cardiovascular studies are available to us in all but 15 of the 211 subjects. All but three of these 15 are doctors, now in good health, who have promised to return for reexamination, but who have not yet done so.

In both these groups, we know with certainty whether each subject is alive or dead. Nor do we think that there is much danger of our being seriously mistaken in determining the presence or absence of serious heart disease in any case, but in doing the statistical analysis of this aspect of our results, we have given most attention to the maximum-contact group of 122 persons. To add the data secured from the remainder causes no change in our conclusions.

Our Subjects' Health at the Time of the First Test

No one with a history of rheumatic fever was admitted to the series. All were actively working at the time of the first test and considered themselves to be in good health. Each, when asked whether he knew of any abnormality that would disqualify him from admission to a series of persons normal from a cardiovascular viewpoint, answered, "No," with the few reservations to be mentioned below.

Thus we have two cases of arrested tuberculosis in the series, two of mild diabetes, and one of mild pernicious anemia, asymptomatic on liver extract. In six of the older subjects, the blood pressures taken at the time of the original test were above the old normal standards of 150/100, but in only one could hypertension be diagnosed by the more modern standards of Master et al.,[8] and in him only the systolic pressure exceeded the normal range.

Two older subjects had suffered from single episodes that might have been mild cardiac infarction; indeed, this was suspected by doctors attending them at the time. In our opinion, however, the evidence was inconclusive, and both survived the 20-year period in excellent health; so we saw no reason to exclude them.

One subject had had an acute episode of substernal pain and electrocardiographic changes suggestive of pericarditis. He recovered, and has had no further cardiac difficulty during the next 25 years. So we saw no reason to exclude him.

Two of our subjects had had a brief attack of atrial fibrillation some years before the first test.

Two persons, examined frequently in the University Hospital during the study, died suddenly and unexpectedly at 67 and 75 years of age. One had had a loud systolic murmur for years, the other developed one before death; so aortic stenosis was suspected, and, if true, some abnormality may have been present when the original test was made.

Table 1

Classification of Final State of Health

		Criteria
Group I.	*Undoubted cardiac disease* Persons thus classified exhibited one or more of these criteria	Cardiac infarction Congestive failure Sudden death without hemiplegia or obvious noncardiac cause Angina pectoris Permanent atrial fibrillation Permanent atrial flutter Physical signs typical of valvular heart disease or pericarditis Permanent complete heart block
Group II.	*Doubtful cardiac status* Persons thus classified lacked any of the criteria listed under group I and exhibited one of these criteria without other evidence of heart disease	Bundle-branch block A-V conduction defect Abnormal orthodiagram Doubtful ECG Suspicious but not diagnostic murmurs
Group III.	*Hypertension* without evidence of cardiac disease. Persons thus classified showed none of the criteria of group I and II	The standards of Master et al.[8] were used.
Group IV.	*No evidence of heart disease or hypertension*	

In summary, the total information now at our disposal indicated that of our 211 healthy subjects one might have had aortic stenosis at the time of the original (1939) test, one may have had mild essential hypertension, two might have had a small coronary occlusion, and one a mild pericarditis before the first test. Of the remaining 206 it seems most unlikely that anyone had any cardiac abnormality, detectable by the clinical tests used routinely today, at the time the first ballistocardiogram was taken.

If these five persons, possibly not completely healthy when the first test was made, are omitted from the series, the conclusions drawn from the statistical analysis of the results are unchanged.

Inspection and Measurement of the Original Ballistocardiograms

Almost all the old records were available for inspection. For those that had disappeared we used the measurements and description in the old record book. Measurement of the vertical distance between the tips of the recorded I and J waves gave the maximum amplitude of each complex. The sum of the amplitudes of typical large and small complexes of the respiratory cycle, which we call $I + J + I_2 + J_2$, defines the amplitude of any record, and we have used this value in the statistical analysis. This value divided by two gives the average amplitude of the ballistocardiogram that appears in the figures. These values are recorded in the tables in millimeters, but they can also be expressed in units of force. Our instrument was kept adjusted so that a deflection of 10 mm. corresponded to 280 Gm. of force, and the relation between force and deflection was linear.

Precautions to Avoid Bias in Analyzing the Results

We doubt if bias can be altogether avoided in any study, but one should take what steps he can to minimize it. To this end the cardiovascular status of the subjects who became ill was decided by Dr. Wood, at a time when he had no knowledge of the ballistocardiograms.

Data concerning the original ballistocardiograms were assembled and analyzed by Dr. Starr. It was impossible to do this without knowledge of the present health of the persons concerned. But the great majority of the records, all except some of those taken on certain medical students during class demonstrations, had been measured many years ago within 24 hours of taking them. So in this study we decided to use the measurements made many years ago rather than to make new measurements that might be biased by knowledge of the outcome.

Accordingly, using the criteria given in table 1, Dr. Wood divided the subjects into the four subgroups shown in that table, in accordance with the changes in their health, if any, that took place during the long study. This classification of the subjects from their after-histories, the age at which each entered the study, the amplitude of the original ballistocardiograms, and the duration

of the follow-up are to be found in tables 2, 3, 4, and 5. Table 4, containing the data on those who died without developing heart disease, and the very long table 5, the data of those who remained healthy, have been filed with the Library of Congress from which they can be secured by anyone interested.*

Results

Mortality

In figure 1, the mortality of the whole group is compared with the expected mortality of a group of similar age and race residing in Pennsylvania. For the calculation of the "life table," which permits this comparison, we are indebted to Dr. Stanley Schor, of the Department of Public Health and Preventive Medicine, who made use of the age-sex-race adjusted Pennsylvania State Life Table 19. This figure shows clearly that the mortality in our group was always less than that to be expected; indeed, the difference is impressive.

The males of this group were next divided into three subgroups approximately equal in size, comprising those with large, medium, and small ballistocardiograms. For each of these three subgroups, the expected mortality was calculated, this time by Dr. Schild, again using the Pennsylvania State Life Tables. In figure 2, this expected mortality can be compared with the actual mortality for each subgroup of our series. As in the series as a whole, there was less mortality than the expected in each of the subgroups studied.

Inspection of the data given in tables 2 and 4, shows that those dying of all causes tended to have small ballistocardiograms when first tested about 20 years ago. Seventy-three per cent of men with original records smaller than 8.5 mm. have died during the period of observation; only 4 per cent of men with records larger than this died during the study. If the eight men dying from causes other than heart disease are omitted, the corresponding figures are 67 per cent and 1.5 per cent. Needless to say, such striking differences are highly significant.

Inspection of the tables shows that mortality among the women is also concentrated in those with small original ballistocardiograms.

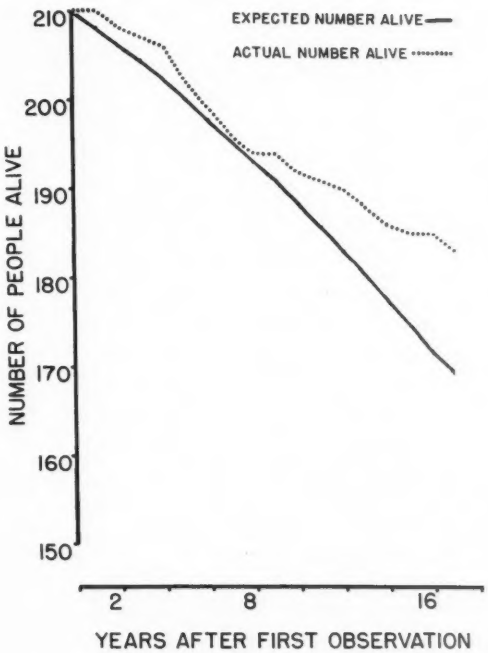

Figure 1

This figure illustrates the difference between actual and expected mortality during the first 17 years after the initial ballistocardiogram, the longest period of time during which everyone in the series of 211 persons was under observation. The solid line indicates the number of our subjects expected to be alive in any year; the dotted line, the number of persons of our series remaining alive. Both men and women have been included in the computation.

Morbidity from Heart Disease

During the long period of observation, 36 of our subjects (table 2) developed "undoubted" heart disease in unmistakable form.

Seven other persons (table 3) developed some cardiac abnormality, which either did not affect their well being, or affected it very little. A few others developed essential hyper-

*Table 4, containing data on those dying of causes other than heart disease, and table 5, data on those remaining in good health, have been deposited as document no. 6564 with the ADI Auxiliary Publications Project, Photoduplication Service, Library of Congress, Washington 25, D.C. A copy may be received by remitting with the order $1.25 for photoprints or $1.25 for 35 mm. microfilm. Make checks or money orders payable to: Chief, Photoduplication Service, Library of Congress.

Table 2

Summary of Those Who Developed Undoubted Heart Disease

Subject	Age at first ballisto (yr.)	Average ballisto amplitude (10 mm. = 280 Gm.) (mm.)	Time of onset after 1st ballisto (yr.)	Time of death after 1st ballisto (yr.)	Pertinent clinical findings and diagnoses
MEN					
D. G.	63	3.5	6	11	Recovered from first attack coronary occlusion; died 5 years later, of another
X. L.	46	4	7	7	Dropped dead at wheel of his auto
X. E.	63	4	3	18	Angina pectoris 15 years; died of coronary occlusion, necropsy
H. B.	59	4.5	2	5	Typical coronary occlusion followed by angina pectoris
G. E.	74	5	3	4	Angina pectoris for 1 year; died of coronary occlusion
G. Y.	58	5.5	17	17	Coronary occlusion, died in first attack, necropsy
X. E. V.	51	6	12	22	Coronary occlusion, angina for years, hypertension, atrial fibrillation; dropped dead sitting in chair
I. G.	57	6	5	5	Developed angina pectoris, later pneumonia with empyema, died suddenly during convalescence; necropsy showed advanced coronary arteriosclerosis and recent infarct of lateral wall of left ventricle
C. O.	55	6	4	4	Developed diabetes and hypertension; died of arteriosclerotic heart disease
D. N. S.	55	6	13	21	Developed murmur suggesting aortic stenosis, later dyspnea on exertion, relieved by digitalis; dropped dead in R. R. station
D. H. B.	85	6.5	2	7	Basal systolic murmur, enlarged heart, abnormal electrocardiogram; diagnosed arteriosclerotic heart disease
S. S.	63	6.5	8	13	Developed hypertension followed by repeated bouts of congestive failure
K. J. D.	53	6.5	7	15	Developed loud systolic murmur at apex and base; dropped dead on street
F. G.	59	6.5	2	12	Typical severe coronary occlusion followed by 2 minor attacks
K. K. T.	44	6.5	7		Developed angina pectoris, exact onset difficult to date, working actively
F. E.	69	7	3	4	Developed angina pectoris; attacks of dyspnea; killed by a fall
T. I.	51	7	11	14	Severe attack of coronary occlusion, later congestive failure; necropsy
D. H. A.	63	7.5	3	13	Had 4 mild attacks of coronary occlusion
I. E. E.	62	8	4	7	Repeated attacks of pulmonary edema; dropped dead
N. E.	65	8	7	7	Acute coronary occlusion, heart ruptured; necropsy
C. N.	48	8	3	17	Acute coronary occlusion followed by angina; necropsy
D. N.	63	8.5	7	10	Developed hypertension and congestive failure
H. P.	44	8.5	13		Typical acute coronary occlusion 13 years after 1st ballisto, good recovery
K. V.	53	10	6		Developed angina pectoris, rare attacks atrial fibrillation, Parkinson's disease
M. L.	50	11	16	21	Developed loud systolic murmur, later atrial fibrillation and repeated attacks of congestive failure; necropsy

Table 2—*Continued*

Summary of Those Who Developed Undoubted Heart Disease

Subject	Age at first ballisto (yr.)	Average ballisto amplitude (10 mm. = 280 Gm.) (mm.)	Time of onset after 1st ballisto (yr.)	Time of death after 1st ballisto (yr.)	Pertinent clinical findings and diagnoses
MEN					
K. J. M.	42	8	16		Developed angina pectoris, Addison's disease, and pulmonary tuberculosis; did well under therapy—still working
G. E. J.	48	11.5	13		Typical acute coronary occlusion, good recovery
H. C. B.	49	15.5	12	14	Mild attack coronary occlusion, later dropped dead in bathroom
X. L.	29	16	19		Mild acute coronary occlusion followed by angina pectoris, working actively
K. J.	32	17.5	19		Developed A-V heart block; working but handicapped
WOMEN					
K. V.	74	4	4		Developed angina pectoris, attacks infrequent, severe arthritis of knees, still alive, age 95
N. N.	51	5.5	6	7	Typical coronary occlusion, recovered, later dropped dead while shopping
F. E. S.	69	5.5	4	18	Attacks of atrial fibrillation; final acute coronary occlusion, ruptured septum; necropsy
F. D.	61	5.5	10		Developed mild congestive failure; free of edema on digitalis and an occasional mercurial; now in psychiatric hospital for senile dementia
F. E.	59	10.5	12		Developed angina pectoris
F. T.	30	13	23		Typical coronary occlusion; good recovery

tension without apparent impairment in their hearts; these are marked in table 5.

Figures 3 and 4 show the relation between the size of the initial ballistocardiogram and the development of undoubted heart disease, a doubtful cardiac status and hypertension in the men and women of our group. These figures show the status at the time the period of observation was terminated, in March 1959, without regard to the differences in duration of the periods of observation. From this arrangement of our data, those dying without developing heart disease (table 4) have been omitted. Obviously heart disease developed with far greater frequency among those with small than those with large ballistocardiograms during the long period of observation, and this difference is highly significant.

Figure 5 illustrates the development of undoubted heart disease in the maximum-contact group. In this figure the data were arranged in order of the size of their initial ballistocardiograms in column A, the dots representing those that developed heart disease; the circles, those that remained healthy in the next 5 years. In column B, we have recorded similarly the onset of undoubted heart disease during the period of the sixth to eleventh years of observation. At the onset of that period, the subject, being 5 years older, would have been expected to have smaller ballistocardiograms for that reason. The expected diminution in amplitude during this period has been calculated from regression equation "a" of table 7, and the symbols for each subject have been moved downward, a distance corresponding to 1.5 mm. on the scale on the left. Column C shows the incidence of onset of undoubted heart disease from the twelfth to the seventeenth years, similarly adjusted for the expected diminution of ballistocardiogram amplitude with age.

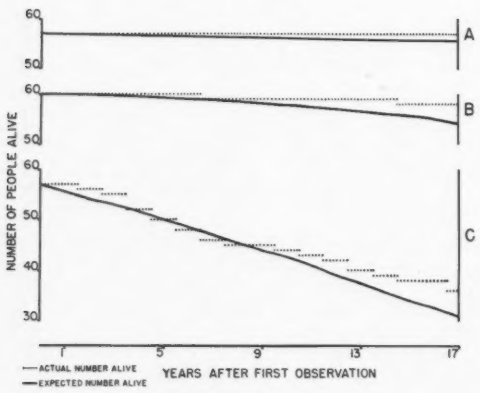

Figure 2

Life expectancy for the 174 men in the series in comparison with the number who actually died during the 17 years of observation. The men have been divided into three groups of approximately equal size. A, those with large ballistocardiograms at the initial test; B, those with middle-sized records; C, those with small records.

What happened in the first 5 years of exposure is very striking. Of those with original ballistocardiograms below 8.5 mm. in average amplitude, 38 per cent developed undoubted heart disease during this period. In contrast, no one with a ballistocardiogram larger than 8.5 mm. developed any cardiac abnormality during the first 5 years; a highly significant difference. Later, presumably accompanied by a diminution of their ballistocardiograms as their age advanced, other cases of heart disease developed in those whose records were expected to fall below this level.

The results secured in the women shown in figure 6 are similar. Again there is one exception to the usual finding.

Discussion

Our subjects, all followed for 17 years and many for longer, had a mortality in every year of the study smaller than that to be expected from the actuarial tables of life expectancy. Indeed, at the end of the 17-year period of exposure common to all, the deaths numbered less than two thirds of those expected. It was indeed an unusually healthy group that provided the subjects for this study.

As is so generally the case with healthy persons, the form of the initial ballistocardiograms of our group was normal with few exceptions. So no information concerning the significance of abnormalities of ballistocardiographic form, the abnormality so commonly found in patients, can be derived from this study. The significance of abnormalities of form, touched on in an earlier paper,[9] has been studied again and will be reported in a paper to follow this, which will be concerned with the after-histories of the patients we have been able to follow for long periods.

In this laboratory, our records have always been calibrated, so that we can determine not only abnormalities for form, but also abnormalities of amplitude. The first reflects chiefly the coordination of the cardiac contraction; the second, chiefly its strength. So we have arranged our subjects according to the strength of the heart's beating, in order to compare each subject's position in the arrangement with his after-history.

During the 23 years of the study, however, there has been a marked improvement in ballistocardiographic instrumentation. Our original instrument, the best of its kind for almost 20 years, is now outdated. Yet it seems evident that this has no effect on the conclusions we are prepared to draw from its records. To permit a comparison between the old and new records, ballistocardiograms taken within 15 minutes of one another have been secured on a large number of persons by (a) our original instrument, (b) our modern high-frequency instrument, and (c) our ultra-low frequency instrument. All these records were calibrated in terms of force. Statistical analysis of 50 consecutive tests of this kind demonstrates that the over-all amplitude of records secured on our old instrument is significantly larger than that of either of our more modern instruments. But, while the absolute values are significantly different, the correlation between amplitudes of ballistocardiograms secured on the same subjects by old and more modern methods is very strong indeed; thus, when one compares the old and the modern high-frequency records, $r=0.91$; comparing

Table 3

*Summary of Those Whose Cardiac Status Could Not Be Passed As Altogether Normal. The Group Called "Cardiac Status Doubtful"**

Subject	Age at 1st ballisto (yr.)	Average amplitude at 1st ballisto (10 mm. = 280 Gm.) (mm.)	Pertinent clinical findings and diagnoses
N. O.	49	5.5	Developed hypertension, occasional paroxysms of tachycardia; exercise tolerance good
P. J. S.	53	8.5	Attacks of atrial fibrillation for 20 years, has developed gout and slight hypertension; good exercise tolerance
X. D.	30	10	Right bundle-branch block developed between 1951 and 1957; no history of onset, no other evidence of heart disease; extremely obese
F. F. E.	60	10.5	Left bundle-branch block, brief attack of atrial fibrillation. Exercise tolerance good for his years; heart normal size
F. D. N.	54	11	Developed systolic apical murmur and slight cardiac enlargement; exercise tolerance good
F. R. S.	43	11	Right bundle-branch block, developed between 1951 and 1958; no symptoms nor other evidence of cardiac disease; exercise tolerance excellent
N. G.	39	11	Labile hypertension, enlarged cardiac silhouette, normal exercise tolerance

*All had a complete cardiovascular examination including electrocardiogram and fluoroscopy that was negative except for the findings mentioned.

the old high-frequency and the modern ultra-low frequency records, $r=0.86$, the two coefficients not being significantly different. The regression equations are given in table 6. These highly significant correlations are almost identical with the test-retest correlation, $r = 0.905$, secured by Tanner[16] for our old high-frequency instrument. Therefore, while the numerical values for amplitude given in the figures will not apply exactly to results secured by a modern method, there is every reason to believe that, if our original records had been secured by any good modern method, the persons of our series, if arranged in order of their record's amplitude, would be in essentially the same order as is shown in our figures. So, our conclusions, based on this order and not on absolute values, should be found valid for records obtained by modern instruments.

In any study of the significance of such an arrangement, the women and men should be treated separately, for women have ballistocardiograms smaller than men, not because they are smaller in size, but because they are women.[10-12]

As soon as the men and women of our series are arranged in order of the average amplitude of their records, one important fact becomes obvious immediately: there is a very strong relationship between the ages of the subjects and the amplitudes of their ballistocardiograms. This has long been known,[4, 10, 11] but we now have additional information. The facts about this important relationship and their significance must now be discussed in detail.

Age and the Amplitude of Ballistocardiograms

It is a well-known axiom of mathematical logic that two quantities, each equal to a third, are equal to one another. One can also say with confidence that two series of measurements, each positively correlated with a third series, are probably correlated with one another. For this mathematical reason alone, since the incidence of coronary heart disease increases with age, it is to be expected that any series of measurements found to be strongly correlated with the later development of coronary heart disease, will also be found to be correlated with age. Indeed, if any plan proposed for the prediction of heart

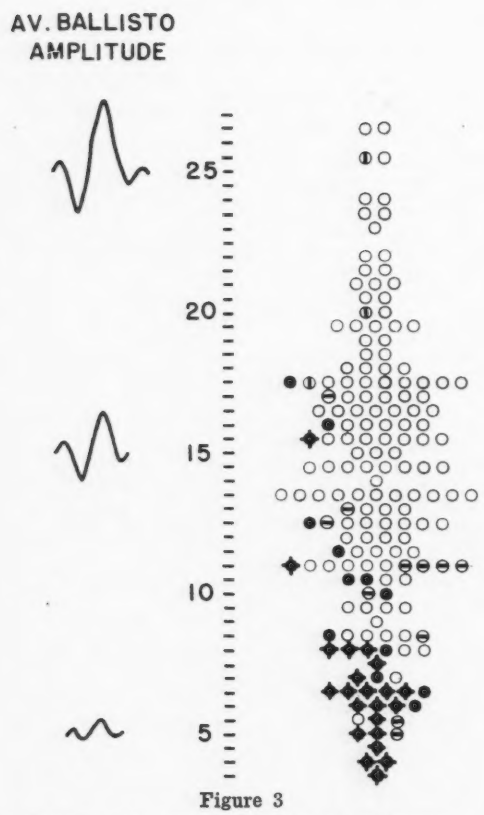

Figure 3

Relation of the size of the original ballistocardiogram to the development of undoubted heart disease, a doubtful cardiac status or hypertension diagnosed according to the criteria given in table 1. The exact diagnosis of each case who developed heart disease can be found in table 2 or 3. This figure shows the status of the group of men as of March 1959, when the series was closed. The eight persons dying from causes other than heart disease are omitted from this figure. Circles, no heart disease developed; dots, those who developed undoubted heart disease, crosses superimposed indicate that they died from it; horizontal bars, those who developed a doubtful cardiac status; vertical bars, those who developed hypertension without evidence of heart disease.

disease did not provide data that correlated with age, the plan might properly be regarded with suspicion.

The amplitudes of ballistocardiograms, strongly correlated with the later development of heart disease in our data, are also strongly correlated with the ages of our subjects. The regression equations relating these amplitudes to the ages of the 174 men in our series were calculated for us by Dr. Schild, and the results are given in table 7. The correlation coefficient is 0.74, values of 0.25 being significant for $p = 0.01$.[13] Therefore, the possibility that chance might account for this association is altogether negligible. Young people tend to have ballistocardiograms conspicuously larger than those of old people.

Both previous studies[11] and inspection of the dot diagram itself, however, suggested that the regression might be slightly curved. Accordingly, we tested the relation between age and the square root of the amplitude of the ballistocardiograms. In our 174 male subjects $r = 0.77$, a value a little higher, but, tested by Fisher's z transformation,[13] not significantly different from the previous correlation.

Some of the 174 males in our series, however, developed heart disease during the study, and in these our data indicate that some abnormality was present when the initial ballistocardiogram was made.

So Dr. Schild was also asked to calculate regressions for those of the maximum contact group who lived for 17 years after their first ballistocardiograms without developing any form of heart disease. These results are given as equations a and b in table 8 and the corresponding dot diagrams are in figures 7 and 8. Any possibility of incipient heart disease having been eliminated by the long follow-up, we regard these regressions as providing the best definitions of relations between age and ballistocardiogram amplitude in healthy persons, and we find them of great interest.

Our findings can also be compared with information about the decline of other physiologic functions as age advances. Figure 9 is based in part on a figure given by Strehler and Mildvan,[14] which illustrates the decline with age of basal metabolic rate, nerve conduction velocity, maximal breathing capacity, standard glomerular filtration rate, and cardiac output per minute per kilo of body

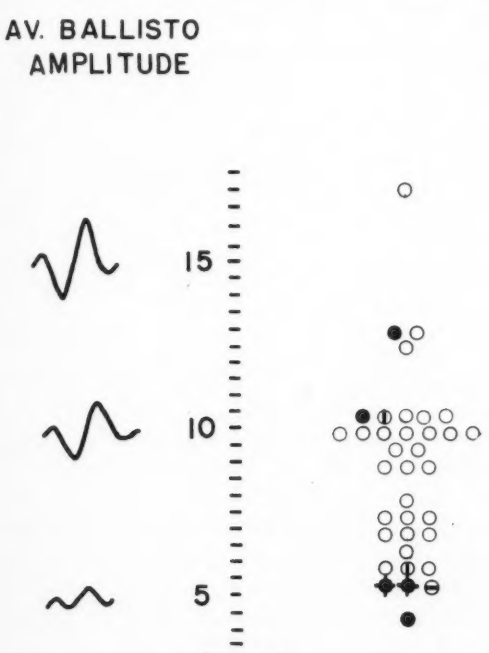

Figure 4

Relation of the size of the original ballistocardiogram to the development of heart disease in women. Status of the group in March 1959. Those dying from other causes than heart disease have been omitted. The period of observation ranged from 17 to 23 years. Symbols as in figure 3.

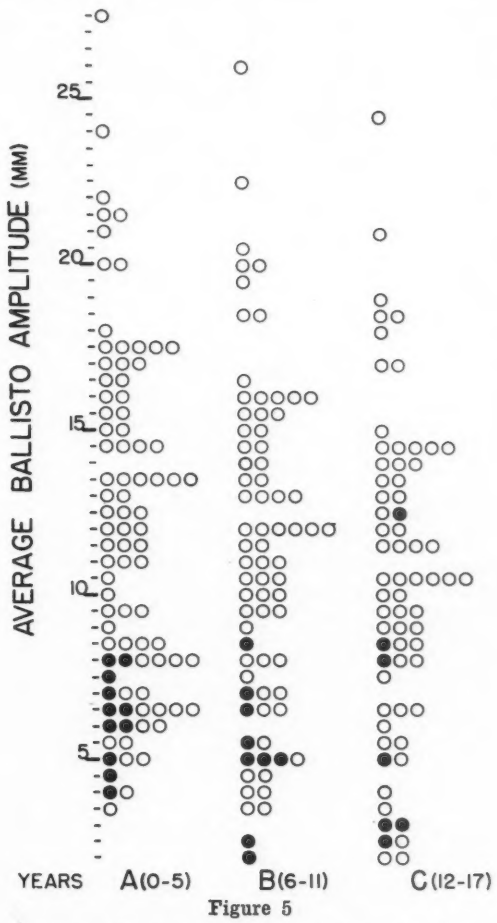

Figure 5

Relation between age *and the* development of undoubted heart disease *in men of the maximum contact group. The adjustment for advancing age is explained in the text. Column A. Dots = those developing undoubted heart disease within 5 years after entering the study. Circles = those living during the first 5 years of the study without developing any type of heart disease. Column B. Dots = those developing undoubted heart disease within the period between 6 and 11 years after they entered the study. Circles = those living 11 years without developing any type of heart disease. Column C. Similar data for the period 12 to 17 years. As one passes from A to B and from B to C, the total number diminishes as the data of persons dying without developing heart disease are withdrawn.*

weight. These authors express the decline of these functions with age by the per cent of the reserve capacity remaining at different ages. The relation between age and ballistocardiogram amplitude, given by equation a, table 7, can be expressed the same way, and this has been shown as the line AB in figure 9, where it lies in the midst of other measurements. So our findings for the heart are in close agreement with what is known about the aging of other bodily functions. According to our data, the reserve capacity of the heart of healthy persons diminishes at a rate of 1.4 per cent per year. Strehler and Mildvan's estimates of the rate of loss of the other human physiologic reserve capacities with age, range from 0.5 to 1.3 per cent per year. So the heart seems to age a little faster than the other organs about which we have this information. The difference is too small to carry weight, but it is consistent with the fact that,

Table 6

*Relations between the Amplitude of Modern Ballistocardiograms and the Instrument Used When This Study was Initiated Over Twenty Years Ago**

Equation number	Regression equation	Standard deviation of the data about its mean (mm.)	Standard deviation about the regression (mm.)	Correlation coefficient
a	B = 375 + 0.736 A	7.0	2.9	0.91
b	A = −0.378 + 1.12 B	8.7	3.6	0.91
c	C = 5.27 + 0.537 A	5.4	2.7	0.86
d	A = −2.19 + 1.39 C	8.6	4.3	0.86
e	C = 3.91 + 0.66 B	5.3	2.6	0.87
f	B = −0.109 + 1.16 C	7.0	3.4	0.87

*Data from 50 subjects studied on each of three instruments at 15-minute intervals. A = values secured by the original high-frequency instrument; B = values secured by the modern high-frequency instrument; C = values secured by the modern ultra-low frequency instrument. The amplitudes were measured in millimeters and these values were used in the calculations. A deflection of 10 mm. corresponds to a force of 280 Gm. in each instrument.

in older persons, death is attributed to heart disease more frequently than to disease of any other organ.

On the Physiologic Age of the Heart

It is a truism that some grow old before their time, as if the aging process progressed unduly rapidly. The conception can also be applied to the organs and the idea of the unduly aged heart is a familiar one to the medical profession. But we know of no previous attempt to give exact expression to the heart's physiologic age.

When the amplitude of the ballistocardiogram is known, physiologic cardiac age can be calculated for each of our male subjects from equations g or h of table 8, which were derived by solving regressions a and b of that table, for age. The two equations give very similar, but not identical estimates of physiologic cardiac age, and we do not know which is the more useful. We have not calculated similar regressions for the women of our series because of their small numbers, but similar equations calculated from other data[11] might be used. For records secured by any modern instrument, an equation to give the physiologic age of the heart of any subject could be derived by combining equation g or h of table 8 with the equation of table 6, which pertains to the type of modern instrument being used.

As far as the statistical analysis of our data is concerned, it makes no difference to the conclusions whether or not we use the amplitude of our record directly or after converting it into physiologic age. However, knowledge of the physiologic age of the heart of each subject permits us to explore the possible advantage of using physiologic age, instead of chronologic age, to enter standard life expectancy tables.

Studies on the Relation between Chronologic Age and Physiologic Cardiac Age as Judged by Ballistocardiogram Amplitude

In the upper half of figure 7 is the dot diagram showing the relation between age and average ballistocardiogram amplitude for the men of the maximum contact group who remained healthy, and its equation is given, in slightly different form, in table 8. This same regression is placed in the lower half of figure 7 together with the dot diagram and regression of those who developed undoubted heart disease. Obviously, the dots representing those who developed heart disease do not conform to the regression of those who remained in health. In figure 8, similar to figure 7 except that age is related to the square root of amplitude, the distinction between the "normals" and the "cardiacs" is even clearer.

Inspection of figures 7 and 8 shows that the "cardiacs" and "normals" do not cover

Table 7

*Relation of Age to Ballistocardiogram Amplitude. Data from 174 Males**

Equation number	Regression equation	Standard deviation of the data about its mean	Standard deviation about the regression	Correlation coefficient
a	$(I + J + I_2 + J_2)$ mm. = 46.9 − 0.528 Age Years	10.6 mm.	7.1 mm.	−0.74
b	Age Years = 65.4 − 1.04 $(I + J + I_2 + J_2)$ mm.	14.9 years	10.0 years	−0.74
c	$\sqrt{I + J + I_2 + J_2}$ mm. = 7.08 − 0.053 Age Years	1.03 mm.	0.65 mm.	−0.77
d	Age Years = 94.1 − 11.2$\sqrt{I + J + I_2 + J_2}$ mm.	14.9 years	9.5 years	−0.77

*$I + J$ = vertical distance between peaks of I and J waves of largest complex of respiratory cycle: $I_2 + J_2$ = same distance for smallest complex of respiratory cycle. The values are in millimeters when 10 mm. = 280 Gm.

the same age range, and a certain advantage is gained, though something is also lost, by restricting the comparison to the age range both have in common, 43 to 65 years. The regression equations of the normal subjects within this range are also given in table 8 for this reason.

That the cardiac group is significantly different from the normal group can now be demonstrated in two ways. First, the slope of the regressions of the cardiac group, equation e of table 8, is found to be significantly different from those of the regressions of the whole normal group, equation a, ($t = 3.6$); and also from that of the restricted normal group, equation c, ($t = 5.3$).

Second, from the age of each subject and from equation c of table 8, an expected ballistocardiogram amplitude can be calculated for each "cardiac" subject in the common age range from the data secured on those who remained healthy. This expected amplitude was paired with the amplitude found for that subject, and the difference determined. The ballistocardiogram amplitude found for the 24 "cardiacs" in the common age range averaged 4.8 mm. smaller than the expected, for this difference $t = 4.24$, so the difference is highly significant.

We can now go further and classify the cardiac subjects according to the time required to develop heart disease. The eight who developed cardiac disease within 5 years gave initial ballistocardiograms that should have averaged 32 per cent larger than the value found, a significant difference, $t = 3.05$. For eight who developed cardiac disease between 6 and 10 years, their ballistocardiograms should have averaged 38 per cent larger than was found, but because of greater scatter conventional significance was missed by a narrow margin, $t = 1.77$. Among the eight who developed cardiac disease between 11 and 17 years after the first test, their ballistocardiograms should have averaged 26 per cent larger than the values found, another significant difference, $t = 2.09$. It should be noted that a higher significance was found for those who developed heart disease soon than for those who developed it later, as one would expect.

Paired Experiments

We next sought to neutralize the effect of chronologic age by pairing the subjects with one another.

A *cardiac group,* all men and women, who developed undoubted heart disease within 17 years after the first test, and a *control group,* those of comparable age who lived 17 years after their first ballistocardiogram without developing either undoubted heart disease or a doubtful cardiac status, were arranged according to their age at their entrance into the study; as in table 9.

Inspection of table 9 shows that in pairing these data we had to make several choices and the problem was to make them without bias. Since inspection of table 9 seemed to indicate that the controls—those who did not develop heart disease—had larger ballistocardiograms than those of similar age who did, this hypothesis was set up and the

Table 8

*Regression Equations Relating the Age of the Subjects of the Maximum-Contact Group and the Amplitude of Their Original Ballistocardiograms**

Group studied	Equation number	Regression equations	Standard deviations of the data		Correlation coefficient
			about its mean	about the regression	
Normal Group					
Those not developing heart disease n = 59	a	$B = 48.8 - 0.54\ A$	9.4	6.9	0.68
	b	$\sqrt{B} = 7.3 - 0.05\ A$	0.90	0.65	0.70
Those not developing heart disease aged 43-65 inc. n = 20	c	$B = 59.4 - 0.73\ A$	6.7	4.8	0.69
	d	$\sqrt{B} = 8.9 - 0.08\ A$	0.71	0.49	0.73
Cardiac Group					
Those developing undoubted heart disease in 17 years n = 27	e	$B = 23.6 - 0.16\ A$	5.0	4.8	0.30
	f	$\sqrt{B} = 4.9 - 0.02\ A$	0.62	0.60	0.30
Normal Group					
Those not developing heart disease n = 59	g	$PA = 90.4 - 1.85\ B$			
	h	$PA = 146 - 20\sqrt{B}$			

*A = Chronologic age (years); P = Physiologic age (years); B = Ballistocardiogram amplitude (mm. when 10 mm. = 280 Gm.). As our measure of amplitude the sum of the amplitudes of I and J waves of typical small and large complexes of the respiratory cycle has been used.

choices made so that they would tend to defeat it.

Thus, in our first calculation, pairs were made according to the following rules. 1. For every cardiac case a control was sought of the same calendar age; if none was available, a control 1 year older was used; or, if none was available, a control 2 years older. 2. When there were two pairs of the same or comparable ages, which individual was paired with which was decided by tossing a coin. 3. When, within one age group, more than one cardiac had to be compared with only one control, or vice versa, an average value was used to pair with the single value. 4. No datum was used twice.

By means of these rules, 16 pairs of men were secured and one cardiac, I.E.E., had to be left without a mate. Similarly, two pairs of women were secured; and for one cardiac woman, F. E., no control could be found.

In each pair we now subtract the average ballistocardiogram amplitude of the cardiac subject from that of the control and so obtain a series of differences. The averages of these differences would approach zero if the cardiac group and the controls tended to have ballistocardiograms of similar amplitude. So we can now ask ourselves the question, is the mean of the differences we find significantly different from zero. For the 16 pairs of men, the mean difference in ballistocardiogram amplitude is 3.0 mm., the controls having the larger values; $t = 3.07$, so the likelihood of chance explaining the findings is negligible. If one adds the two pairs of women, the mean of the differences is 2.75 mm. in favor of the controls and $t = 3.13$.

Two more pairs can be secured by using two persons, F.E.E. and F.D.N., from the doubtful cardiac status group (table 3) as controls. This seems a reasonable thing to do for both subjects consider themselves to be in good health at present and both have an exercise tolerance excellent for their age of 76 and 80 years. This gives us 20 pairs, and

the mean difference in ballistocardiogram amplitude is now 2.95 mm. in favor of the controls. This is a striking difference, after thus neutralizing the effect of age, the ballistocardiograms of the "cardiacs" still average 25 per cent smaller than those of controls. For these 20 pairs t = 3.64.

To assure ourselves that unconscious bias did not enter into the high significance of the results given above, we now, with conscious bias, selected our pairs in every way possible to defeat the hypothesis that, with age neutralized, the ballistocardiograms of the controls were larger than those of persons who would later develop heart disease. Wherever, in the previous study, we had paired the data of one control with the average of that of several cardiac subjects, we now paired the control with the cardiac subject with the largest ballistocardiogram, and did not use the data of the others at all. Conversely, when one cardiac person had been paired with several controls, the control with the smallest ballistocardiogram was now used, and the others were discarded. When thus weighted against the hypothesis with all the bias we could muster, the mean difference for the 16 pairs of men first studied was still 2.03 mm. in favor of the controls and t = 2.23, a value still significant.

So we must conclude that, with age neutralized, persons who will live 17 years without developing heart disease are still likely to have larger ballistocardiograms at the beginning of that period than those who will develop heart disease.

Pairs of another sort can also be made. Nine of those who developed undoubted heart disease during the period of observation have a ballistocardiogram amplitude that can be matched exactly with that of one or more subjects of the same sex who remained healthy. Three more pairs are secured by using members of the doubtful group as controls, an addition justified by the fact that their general health and well-being are altogether normal. However, as more than one control is usually available, a choice must be made and the difficulties, discussed before, apply.

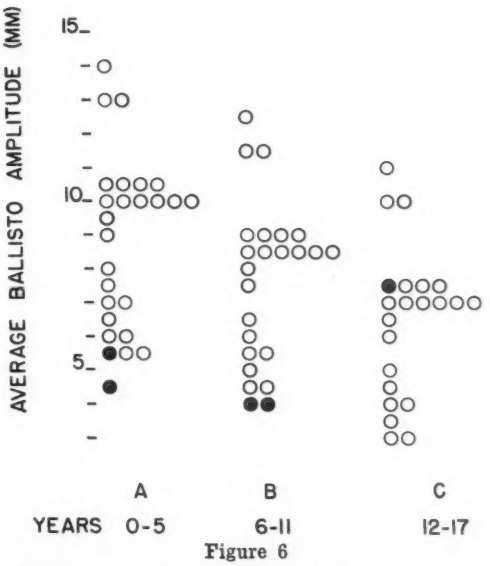

Figure 6

Relation of amplitude *of the initial ballistocardiogram to the* development of undoubted heart disease *in women of the maximum contact group. The adjustment of amplitude for columns B and C is explained in the text. Columns and dots as in figure 5.*

By use of the average of all where more than one value is available, when ballistocardiogram amplitude and sex are thus paired out, those who developed undoubted heart disease average 15 years older than those who remained healthy, and t = 7.04, a striking finding. When one chooses one mate for each cardiac subject with maximum conscious bias against the hypothesis that the ages are different the cardiac group averages 7 years older, and t = 2.56, and this is still significant. So, there is no reasonable doubt that, in our series, when the amplitude of ballistocardiograms are equal, the older person has a greater likelihood of developing undoubted heart disease. This is further evidence that chronologic age and ballistocardiogram amplitudes, though strongly correlated, do not represent the same physiologic aspect of our subjects.

Interquartile Ranges

In column A of figure 5 the data from men developing heart disease within 5 years, and

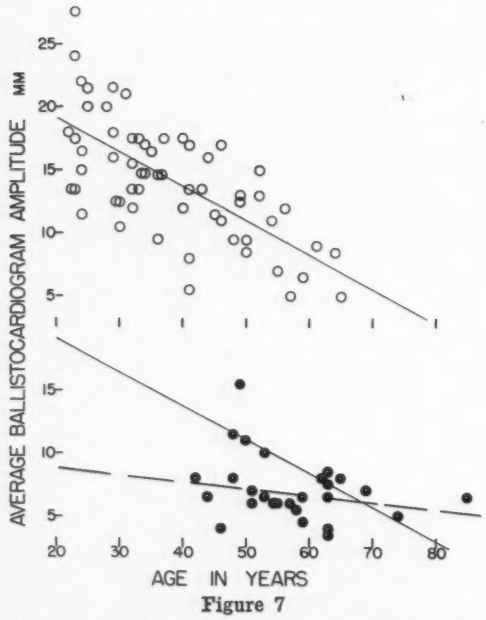

Figure 7

Relation of ballistocardiogram amplitude and chronologic age. Circles represent data from the men of the maximum contact group who remained healthy for 17 years after the result recorded here. Dots represent data from the men of the maximum contact group who developed undoubted cardiac disease during the follow-up period. The solid line is the regression of the circles; it is repeated in the lower half of the figure to permit easy comparison with the regression of the dots, the broken line.

from those who remained well for that period, are arranged according to the amplitude of their ballistocardiograms at the initial test. The interquartile range of the "cardiacs" in this group is 30.3 per cent of that of the whole group. If the same data are arranged according to the chronologic ages of the subjects, the corresponding value is 43.5 per cent.

Corresponding values for those who developed cardiac disease from 6 to 11 years after the initial test, are, when arranged by ballistocardiogram amplitude, as in column B of figure 5, 28 per cent; when arranged by age, 67 per cent. For those who developed heart disease from 12 to 17 years after the initial test, when arranged by amplitude, as in column C of figure 5, this value is 44 per cent; when arranged by age, 61 per cent. The arrangement by amplitude of ballistocardiogram always results in a more compact group of those who are to develop heart disease than does the arrangement by age; so physiologic age, derived from this amplitude, should serve better than chronologic age to identify those who will become abnormal.

Other Statistical Studies

Extensive studies by biserial correlation, and by the chi-square technic supported, but did not add to the conclusions to be drawn from the studies already given; so these results will not be given in detail. The relation between ballistocardiogram amplitude and the later development of heart disease was always at least as strong as that with age, but there was often no simple way of testing for the significance of the difference.

The Ballistocardiogram Amplitude as an Indicator of Mortality

Diminishing conspicuously with age, ballistocardiogram amplitude is a successful predictor of mortality; the question is, does it do so better than age itself. Our attempt to answer this question has been limited, for the moment, to comparisons between the mortality found in our series and that expected from the life table, as is shown in figures 1 and 2. It is difficult to interpret these findings, for it must always be remembered that the life table indicates the mortality to be expected, not in healthy persons as in our series, but in the whole population, both sick and well. In our data, only for the period between 5 and 9 years does the mortality of those with small ballistocardiograms go below the value expected, and even here the difference is small; so it would appear that we were better at predicting morbidity than mortality. In another series,[15] the excess mortality of cases with angina, that is the mortality in excess of that to be expected from their age, was only 7 per cent for men and 5 per cent for women, values, we believe, much less than most doctors would expect; and this is true in our cases also. The after-histories of our hospital patients, in a study now nearing completion, contain many more deaths than

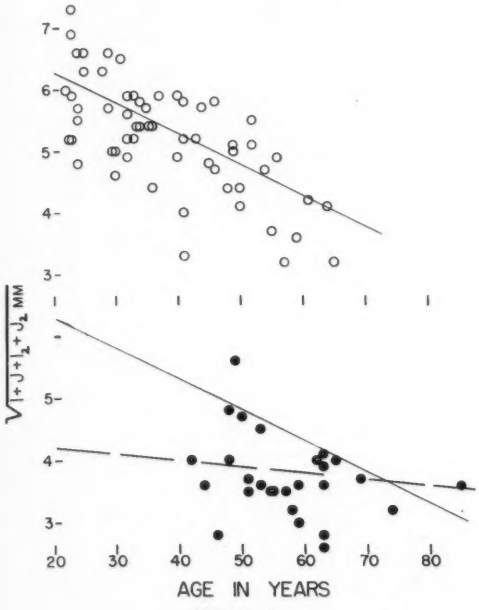

Figure 8

Relation of the square root of ballistocardiographic amplitude and chronologic age. The symbols and lines are similar to those of figure 7.

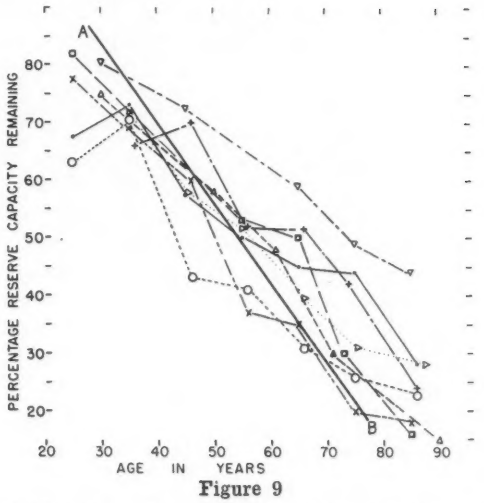

Figure 9

Decline in cardiac and other bodily functions as age advances calculated as per cent of reserve capacity remaining. The solid line A.B. represents the decline of cardiac function as calculated from our data according to the method of Strehler and Mildvan. The other data have been taken directly from those assembled by Strehler and Mildvan. Triangles point down = standard cell water; squares = standard renal plasma flow; triangles point up = basal metabolic rate. X's = maximum breathing capacity; dots = nerve conduction velocity. Circles = cardiac output per beat; crosses = standard glomerular filtration rate; triangles point right = vital capacity.

occurred in this series of healthy persons and give promise of throwing much more light on the relation of the ballistocardiograms to mortality. Further discussion will be deferred until these data can be analyzed.

Final Remarks Concerning the Physiologic and the Chronologic Age of the Heart and Its Relation to the Development of Coronary Heart Disease

So many interesting studies can be performed on a body of data as unique as this, that it is difficult to know where to stop either the statistical analysis or the discussion. For this reason the complete data have been filed in the Library of Congress so that anyone interested could secure them for further study. With several general comments we will bring this report of the present study to a close.

Inspection of figures 7 and 8 shows that, in sharp contrast to the results secured on those who remained in health, in the group who later developed cardiac disease the regression of ballistocardiographic amplitude with age is almost flat; indeed, the slope is not significantly different from zero. So in the cardiac group we have failed to demonstrate a significant relation between the cardiac forces, as measured by ballistocardiographic amplitude, and chronologic age. One wonders if there is not a level below which the cardiac forces cannot go, if the patient is to survive in health. Those that are to develop heart disease, whatever their chronologic age, are all so close to this lower limit that the normal relation between age and these forces has been lost.

Finally we must discuss the meaning of our results in terms of present knowledge of aging, and of the heart disease that so often develops as age advances. Our finding that ballistocardiograms of persons later to develop heart disease, are significantly smaller

Table 9

Data Available to Neutralize Effect of Age by Pairing the Observations

Age at 1st ballisto (yr.)	Cardiac group: Those developing undoubted heart disease within 17 years. Initials and average ballisto amplitude (mm. when 10 mm. = 280 Gm.)	Control group: Those living 17 years without developing any cardiac abnormality. Initials and average ballisto amplitude (mm. when 10 mm. = 280 Gm.)
MEN		
44	K.K.T. 6.5; H.P. 8.5	D.H.V. 16
45		T.O. 11.5
46	X.L. 4	G.E. 17; E.O. 11
47		
48	C.H. 8; G.E.J. 11.5	K.C. 19
49	H.C.B. 15.5	E.M. 13; H.R.P. 12.5
50		U.I.P. 17; E.Y.Z. 9.5
51	T.I. 7; X.E.V. 6	
52		N.L. 15; P.E. 13
53	K.J.D. 6.5; K.V. 10	
54		S.D. 11
55	C.O. 6; D.N.S. 6	S.T. 7
56		B.N. 12
57	I.G. 6	K.R.W. 5
58	G.Y. 5.5	
59	H.B. 4.5; F.G. 6.5	H.V. 6.5
60		
61		B.P.V. 9
62	I.E.E. 8	
63	X.E. 4; D.N. 8.5; D.G. 3.5 D.H. 7.5; S.S. 6.5	
64		F.N. 8.5
65	N.E. 8	I.E.Z. 5
WOMEN		
51	N.O. 5.5	
53		N.L.K. 6.5
69	F.E.S. 5.5	N.D.V. 6

than those of the controls, is consistent with the view that the disease process, which later advanced until it produced characteristic symptoms, was present at the time of the first test to a degree sufficient to weaken the cardiac forces, but insufficient to cause the typical picture of disease. We believe this is the interpretation that would occur first to most doctors, especially since the hypothesis is consistent with the recent evidence that coronary heart disease occurs more frequently in younger persons than was formerly supposed.

Nevertheless, while we cannot deny the possibility that incipient coronary arterial disease accounted for our findings in the "cardiac" cases, we are more inclined to interpret our results from another viewpoint which is in better accord with our findings in the healthy persons of our series. Here we must pause to emphasize the strength of our position. Our belief that these persons were indeed healthy at the time of our tests is based, not only on the usual clinical studies which, alas, are so often inadequate for the detection of incipient disease, but also on the long after-histories. In these cases we know that no manifest heart disease developed for 17 years or longer. We know of no other clinical study providing such strong evidence that those we classify as free of heart disease at the time of our test, were so in truth.

Despite their excellent cardiac health, the decline in the cardiac forces as age advances

is very obvious in these subjects; evidence for it is seen both in the regressions reported here, and in the tests made repeatedly on individuals during the long course of the study. This decline with age is so nearly a universal phenomenon that it cannot be attributed to coronary heart disease, which, though found with increasing frequency as age advances, is by no means always present. So we prefer to think of this weakening of the "normal" heart with age as analogous to the well-known weakening of the peripheral muscles as age advances, a universal phenomenon certainly not to be attributed to scleroses of the supplying vessels. Perhaps chemical or physical in nature, the aging process is doubtless of infinite complexity, and it is not to be identified with any structural abnormality of which we are aware.

With such thoughts in mind we are not ready to attribute the unduly small ballistocardiograms of those who later developed coronary heart disease to the existence of coronary arteriosclerosis at the time of the initial test. We are content with the thought that the hearts of some of our subjects aged more rapidly than those of others, and that, in the former, the heart diseases characteristic of advancing age developed with much greater frequency, as one would expect.

It was the school of James Hope, of Mackenzie, and of Lewis, that for so long emphasized the importance of cardiac muscle function in any consideration of heart disease and its disabilities. The data presented in this paper support the validity of that viewpoint.

Summary

A group of 211 healthy persons, gathered together from 23 to 17 years ago to provide normal standards for the ballistocardiograms, has been followed to the present time. This study is concerned with the group as a whole, or with subgroups. The study of individuals will appear in later communications.

With a few minor exceptions, the group, at the time of the initial test, had ballistocardiograms normal in form. The death rate of the group during the period of the study was much lower than was to be anticipated from standard life expectancy tables for the state of Pennsylvania.

Although the ballistocardiograms of this group were normal in form, there was great variation in the amplitude of the records. Since these records were calibrated in terms of force, this can be interpreted as due to differences in the force of the heart's contraction. Those whose hearts contracted with little force at the initial test later suffered from death and cardiac disability, chiefly coronary heart disease, in far greater numbers than those whose hearts contracted strongly.

The interpretation of this striking finding is bound up with that of another; in our data, as in that of others, there is strong correlation between the ages of the subjects and the amplitudes of their ballistocardiograms. The heart tends to weaken and beat with less coordination as it grows older.

Exact expressions can be given to the "normal" rate of decline of cardiac function with the years by the slope of the regression between age and ballistocardiogram amplitude found in the group of those who remained healthy for 17 years after the test. The normal rate of cardiac decline, as age advances, agrees closely with that calculated for several bodily functions. The cardiac decline seems a little more rapid than that of these other bodily functions, but the difference is small and its significance is doubtful.

In our data, among those who later developed undoubted heart disease, there was no significant tendency for the older people to have smaller ballistocardiograms than the younger.

From the chronologic age of each subject who later developed undoubted heart disease, and the age-amplitude regression of those who remained healthy, one can calculate for each "cardiac" subject, the amplitude expected if he had been in perfect health. On the average this expected value far exceeds the values found. So most of these hearts were performing abnormally for their age although manifest clinical evidence of heart disease had not yet appeared.

When the effect of age is eliminated by pairing the results directly, the relation between the amplitudes of the initial ballistocardiograms and the later development of heart disease remains significant for $p = 0.05$. Indeed, in such pairs with similar ages, those who later developed heart disease had initial ballistocardiograms that averaged 25 per cent smaller than those of their mates who remained healthy for the next 17 years. This is additional evidence that the hearts of those who were to develop myocardial disease were, at the initial test, like the hearts of much older normal people; that is, the physiologic age of their hearts far exceeded the chronologic age.

Acknowledgment

The great bulk of the statistical analysis was performed by Dr. Albert Schild. Dr. S. I. Askowitz computed the more elaborate chi squares. The first author did the remainder, and also provided an independent check on the more important computations.

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The Pulmonary Arterial Tree in Atrial Septal Defect

A Quantitative Study of Anatomic Features in Fetuses, Infants, and Children

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With the technical assistance of Noeke Wagenvoort

IN CONTRAST to cases of ventricular septal defect in which pulmonary arterial lesions occur at a very early age, such changes are generally considered to be late phenomena in atrial septal defect. It is well known that pulmonary hypertension, when it occurs as a complication of a defect in the atrial septum, is usually not seen before adult life.[1, 2] The pulmonary arteries are reported to be largely normal when the pressure in the pulmonary circulation is within normal limits.[3] When the pressure is moderately elevated, intimal thickening of small muscular pulmonary arteries with subsequent narrowing of the lumen is believed to be an early change. In the presence of an increased flow, on the other hand, the pulmonary arterial tree in atrial septal defect is dilated,[3] and it has been shown that dilatation of the vessels with stretching of the walls may mask the presence of medial hypertrophy.[4]

In view of the uncertainties regarding the changes in the pulmonary arterial tree, a study was undertaken of the pulmonary arterial branches in fetuses, infants, and children with uncomplicated atrial septal defect.

Material and Methods

Our material was derived from 12 subjects with uncomplicated atrial septal defect (table 1). Three of these were fetuses of 24, 30, and 36 weeks' gestation, one was a full-term stillborn infant, and the ages of the remaining eight ranged from 2 days to 11 years. Data from cardiac catheterization were available in two cases; in one of these (case 11) the pressure in the pulmonary artery appeared normal, and in the other (case 12) there was pronounced pulmonary hypertension. Of the 12 subjects, seven had died from causes not directly related to the cardiac malformation, as follows: prematurity (cases 1 and 2), prematurity and anencephaly (case 3), premature separation of the placenta (case 4), hyaline membrane disease of the lungs (case 5)), duodenal atresia (case 6), and purulent meningitis (case 10). In the last case the atrial septal defect had been closed surgically 10 months before death. Three children died in cardiac failure (cases 7, 8, and 9) and two died shortly after operation, one as a result of a severe cerebral complication (case 11) and one because of pronounced pulmonary hypertension (case 12). The sex distribution was eight males and four females.

Only the right lung was used for histologic study. Sections from five segments of each right lung were stained with Lawson's elastic stain, counterstained by van Gieson's connective-tissue stain.

For evaluation of medial hypertrophy, the mean relative medial thickness and the index of medial surface area were determined by quantitative analysis. The relative medial thickness is the thickness of the media expressed as a percentage of the external diameter of a muscular pulmonary artery. The mean relative medial thickness is the average percentage calculated for 100 arteries.

The index of medial surface area is an index of the ratio of the surface area of the media of muscular pulmonary arteries to the surface area of the pulmonary parenchyma in which these arteries lie. In other words, this index gives an expression of the amount of pulmonary arterial muscular tissue per unit of lung tissue.

The values for both the relative thickness and the index were compared with those found in a control series of fetuses, infants, and young children with normal hearts and lungs, described elsewhere.[5] The technics for determining the mean relative medial thickness and the index of medial surface area were described in detail previously[4] and in outline in a study of ventricular septal defect.[6] The histopathologic analysis was done blindly in that the sections were mixed with those from subjects with other conditions (ventricular

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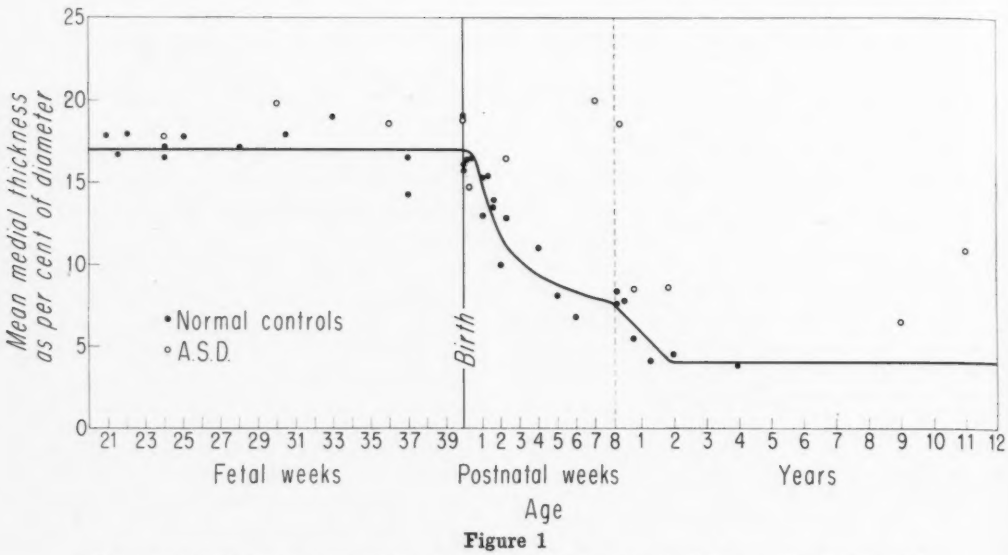

Figure 1

Mean medial thickness expressed as percentage of diameter in 12 cases of atrial septal defect as compared with that in controls of corresponding age. Solid curve is a composite expression of individual control values.

septal defect, aortic atresia, and pulmonary atresia). Neither the nature of the condition nor the age of the subject was known at the time the pulmonary arteries were being measured.

Results

The relevant data obtained for the 12 subjects are listed in table 1. The values of the mean relative medial thickness and the index of medial surface area are shown also in figures 1 and 2, where they are compared with the results in a control group of corresponding ages.

During fetal life and in the newborn period (five cases), the mean thickness of the media was roughly within normal limits (figs. 1 and 3). However, in a 16-day-old infant (case 6), the value was somewhat higher than expected from corresponding data in the control group. In two subjects, 7 weeks and 4 months of age (cases 7 and 8, respectively), the mean thickness of the media reached an extremely high value for this age (table 1, fig. 4). A great number of small muscularized arterioles were present in these subjects (fig. 5). In three cases the medial thickness was at the upper range of normal (cases 9 and 11) or moderately increased (case 10). In the last subject of the series (case 12), who had a greatly elevated pulmonary arterial pressure, pronounced thickening of the media was present.

The index of medial surface area in the three fetuses with atrial septal defect (cases 1 to 3) was high as compared with that in fetuses with normal hearts and lungs (fig. 2). In the stillborn infant (case 4), the index was high but was in the upper range of normal. In five cases of the postnatal group (cases 5, 6, 9, 10, and 11), the index of medial surface area was within normal limits or only slightly elevated. In the three remaining postnatal cases (cases 7, 8, and 12), the index was high, as compared with that of the controls. In case 12, in which pronounced pulmonary hypertension was noted, the index was extremely high (table 1).

Intimal proliferation generally was not an outstanding feature of the muscular pulmonary arteries in the present cases of atrial septal defect. In two patients, aged 7 weeks and 9 months (cases 7 and 9, respectively), a slight degree of intimal thickening was observed in a few branches. However, in case

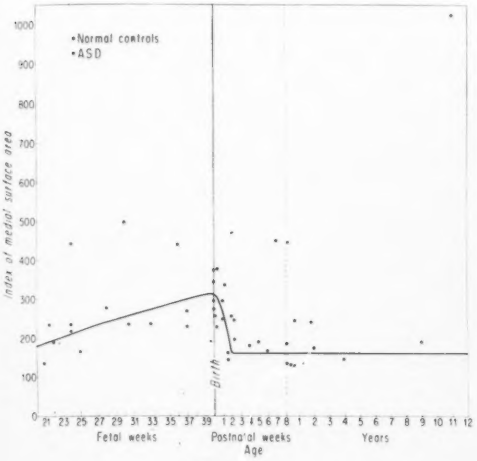

Figure 2

Index of medial surface area in 12 cases of atrial septal defect as compared with that in controls of corresponding age. Solid curve is a composite expression of individual control values.

12, pronounced obliterative lesions were noted in almost every branch (fig. 6*a* and *b*). In addition, two cases (cases 1 and 7) showed moderate intimal thickening of some elastic pulmonary arteries; one of these was a fetus of 24 weeks' gestation (fig. 7). In case 12 the elastic arteries were involved extensively in the generalized obliterating changes. In three patients (cases 8, 9, and 10), there was slight to moderate intimal proliferation in a small number of bronchial arteries (fig. 8*a*). Finally, slight to moderate intimal thickening was sometimes present also in pulmonary veins (cases 8 to 12) (fig. 8*b*).

Plexiform or glomerulus-like structures were numerous in case 12, but were not observed in other cases.

Discussion

In contrast to patients with ventricular septal defect, those with uncomplicated atrial septal defect rarely come to necropsy during infancy or childhood. Consequently, the number of such cases available for study will always be relatively small, and any conclusions drawn from such studies will require special and careful consideration. This is especially true in this series in view of the fact that

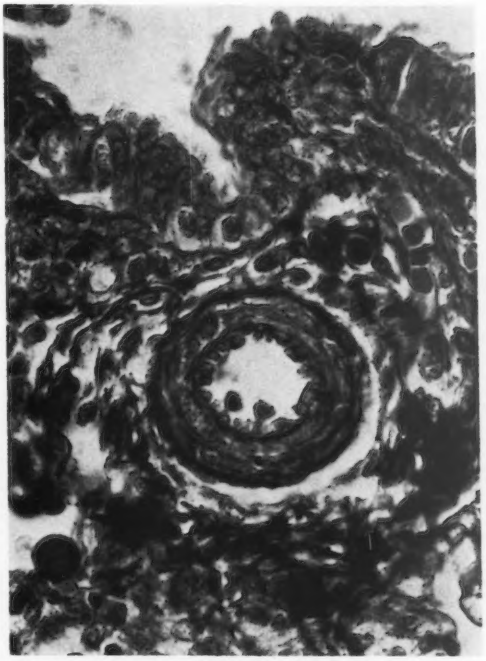

Figure 3

Pulmonary arterial branch in a fetus of 30 weeks' gestation with atrial septal defect. Thick media and narrow lumen are present, but picture is similar to that seen in normal fetuses of corresponding age (elastic stain).

some children died from causes unrelated to the atrial septal defect, and others died from cardiac failure or succumbed shortly after operation on the heart. It is possible that this group of cases does not generally reflect the natural history of the pulmonary vascular tree in atrial septal defect in this age group. This in part may account for some of the unexpected findings with regard to both mean relative medial thickness and index of medial surface area.

In the fetal and newborn periods the mean relative medial thickness did not differ greatly from the normal, although there was a tendency toward values in the upper range of normal. The index of the medial surface area, however, was considerably increased in the three fetuses of the series, indicating medial hypertrophy (fig. 2).

During fetal life the blood that enters the

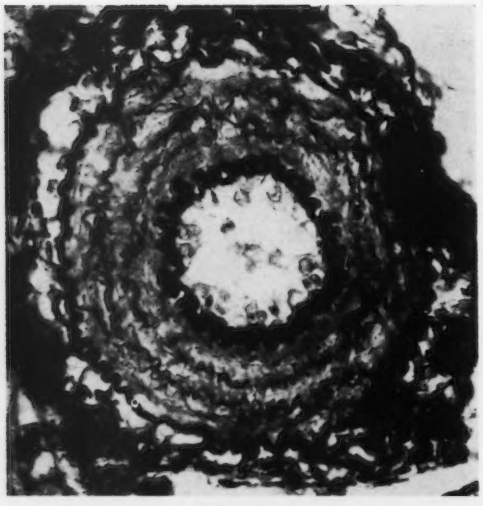

Figure 4

Muscular pulmonary arterial branch in a 4-month-old infant with atrial septal defect. Note extremely thick media with some elastosis (elastic stain).

right atrium flows in part to the right ventricle through the tricuspid valve and in part to the left atrium by way of the foramen ovale. In principle, a defect in the septum will not bring about any appreciable change in hemodynamics. It might be argued that if there is a pressure gradient at the foramen ovale, the presence of a large atrial septal defect might eliminate this gradient. In that case the left atrial pressure would be the same as that in the right atrium and thus higher than it would be in the absence of a defect. This difference in pressures must be small, however, if it exists at all, and it is unlikely to cause important changes in the pulmonary arterial tree.

Although it is possible that the high index of medial surface area observed in the fetuses represented a congenital anomaly of the pulmonary arteries rather than a reaction to hemodynamic changes, it must be admitted that our knowledge of the hemodynamic conditions in fetal life is limited.

It is not surprising that the medial thickness was not elevated in proportion to the increase in the index of medial surface area. In our experience the mean thickness of the

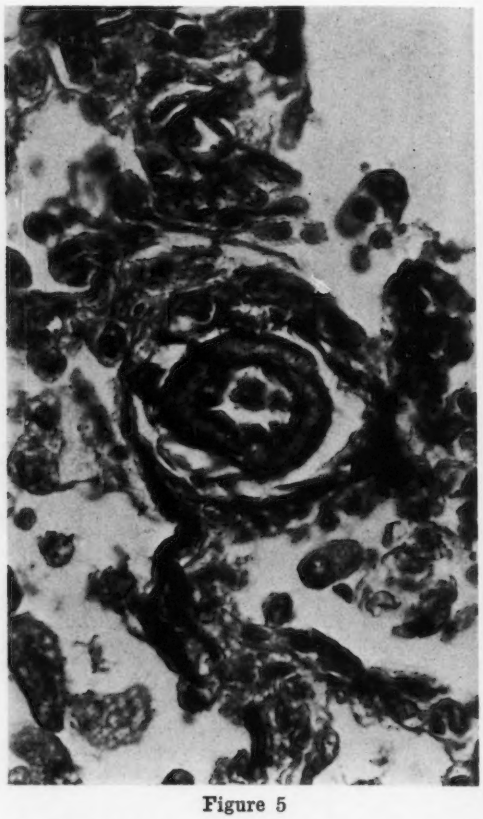

Figure 5

Small muscularized arteriole from the same case as in figure 4 (elastic stain).

media is never much higher than 20 per cent of the external diameter, regardless of age or pulmonary pressure, even though individual arteries may reach a relative thickness of as much as 35 per cent. Apparently, when a mean relative thickness of approximately 20 per cent is reached, increase of the index of medial surface area is brought about by expansion of the muscular coat along the length of an arterial segment rather than by further increase of the thickness of the media.

After the newborn period, the values for the mean relative thickness and index of medial surface area were above the normal values in all subjects (figs. 1 and 2). In two patients, aged 7 weeks and 4 months (cases 7 and 8, respectively), this increase was pronounced (fig. 4). In three others (cases 9,

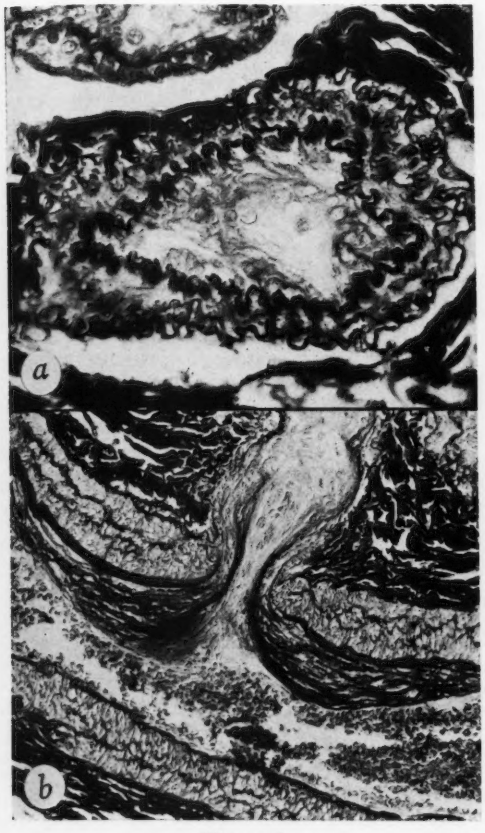

Figure 6

a. *Muscular pulmonary arterial branch, almost obliterated by intimal proliferation, in an 11-year-old child with atrial septal defect. Vessel tends to collapse (elastic stain).* b. *Large muscular pulmonary arterial branch with pronounced medial hypertrophy and intimal proliferation at origin of branch, in same case as in* a. *(elastic stain).*

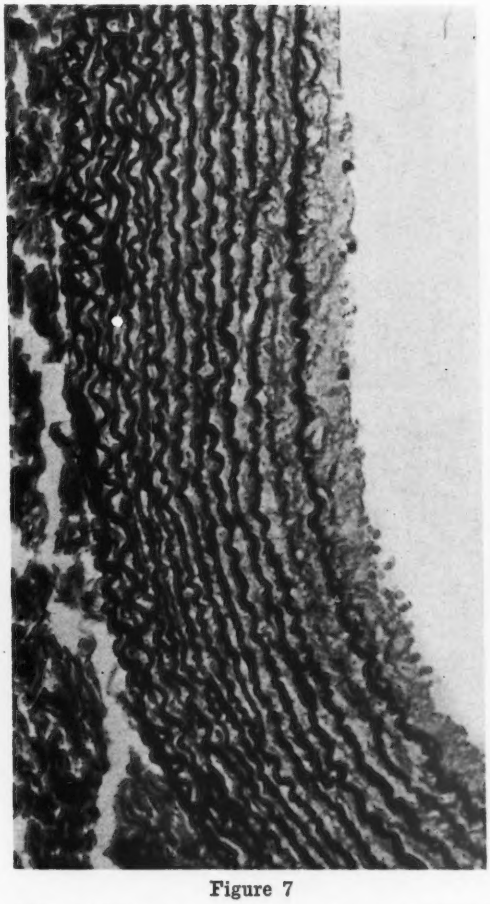

Figure 7

Intimal thickening in elastic pulmonary arterial branch in a fetus of 26 weeks' gestation (elastic stain).

10, and 11), it was slight, sometimes being just within the upper range of normal. The last case, that of a girl of 11 years with pronounced pulmonary hypertension and extensive pulmonary vascular obstructive lesions (fig. 6*a* and *b*), conformed in all respects to the picture seen in adult patients with atrial septal defect complicated by pulmonary hypertension. Apart from the intimal lesions, excessive medial hypertrophy was present.

After birth a left-to-right shunt becomes established in patients with an atrial septal defect, although probably not immediately. This left-to-right shunt results in an increase in the pulmonary blood flow. In spite of this the pulmonary arterial pressure remains normal, since the pulmonary vascular resistance is low.

In the absence of complications the only visible change in the pulmonary arteries in most cases of atrial septal defect is dilatation of the vessels. It seems possible that gradually an increase of the absolute amount of medial tissue occurs as a result of this dilatation. When the cross section of an artery becomes

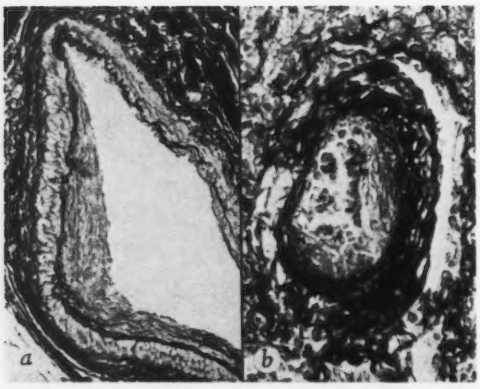

Figure 8

a. *Bronchial artery of a 9-month-old infant with atrial septal defect, showing moderate intimal proliferation (elastic stain).* b. *Intimal proliferation in a pulmonary vein in same case (elastic stain).*

greater, there are fewer medial muscle fibers in this cross section to maintain the pressure. This might well result in a reactive increase in the number of muscle fibers. In any event, dilatation of an artery without such an increase of medial tissue must lead to thinning of the wall as compared to the normal condition. Such thinning has never been described; generally, the relative medial thickness in cases of uncomplicated atrial septal defect has been reported to be normal.[3] A few cases of atrial septal defect in adults have been described; the medial thickness was not far from normal, but the index of medial surface area was considerably increased.[4]

These considerations do not explain the findings in two of our cases (cases 7 and 8), in which both the medial thickness and the index were far above normal values. Although

Table 1

Data in Twelve Cases of Atrial Septal Defect in Fetuses, Infants, and Children

Case	Age, sex	Medial thickness, per cent of diameter	Index of medial surface area	Location and grade of intimal proliferation
1	24 fetal wk. M	17.8	441	Elastic pulmonary arteries; moderate
2	30 fetal wk. M	19.8	495	
3	36 fetal wk. F	18.6	439	
4	Stillborn M	18.8	373	
5	2 days F	14.7	227	
6	16 days M	16.4	245	
7	7 wk. M	20.0	448	Elastic pulmonary arteries; moderate Muscular pulmonary arteries; slight
8	4 mo. M	18.6	444	Bronchial arteries; slight Pulmonary veins; slight
9	9 mo. M	8.5	243	Muscular pulmonary arteries; slight Bronchial arteries; moderate Pulmonary veins; moderate
10	22 mo. M	8.6	240	Bronchial arteries; slight Pulmonary veins; slight
11*	9 yr. F	6.4	188	
12*	11 yr. F	10.8	1024	Pulmonary arteries (elastic and muscular); severe Pulmonary veins; moderate

*Pulmonary arterial pressures obtained by cardiac catheterization in cases 11 and 12 were normal and hypertensive (96/56), respectively.

we are not able to offer any acceptable explanation for these unexpected findings, it should be kept in mind that both children died in cardiac failure, presumably as a result of their congenital cardiac defect. This clinical course, as unfortunate as it is unusual in patients with atrial septal defect of this age, might well be related to, or even caused by, the equally rare (in this age group) pulmonary vascular manifestations.

Intimal proliferation was a feature of several types of pulmonary blood vessels, although it was of a severe nature in only one case. It was found in muscular and elastic pulmonary arteries, in bronchial arteries, and in pulmonary veins. The significance of these changes is not understood except in the subject with pronounced pulmonary hypertension (case 12), in whom these intimal lesions reflected a familiar, although not entirely explained, picture. Intimal proliferation in muscular pulmonary arteries and in pulmonary veins has been described before; it has been attributed to the large flow.[7-9] This may be the explanation in general, but it does not explain the presence of intimal proliferation in one of the fetuses.

Summary

The pulmonary vascular tree was studied in 12 cases of uncomplicated atrial septal defect in fetuses, infants, and children. The ages of these subjects ranged from 24 weeks of fetal life to 11 years. A quantitative analysis was made of the medial thickness and of the index of medial surface area (ratio of medial tissue to pulmonary parenchyma) of the pulmonary arterial branches. In contrast to subjects with ventricular septal defect in corresponding age groups, the three fetuses in this series had medial hypertrophy, as indicated by a high index of medial surface area. In the postnatal group, both the medial thickness and the index of medial surface area were also usually greater than in the controls of corresponding ages, notably in two patients, who, at the ages of 7 weeks and 4 months, died of cardiac failure. No satisfactory explanation for these unexpected findings can be offered.

Slight to moderate intimal proliferation was observed in some muscular and elastic pulmonary arteries, in bronchial arteries, and in pulmonary veins in several subjects. Thickening of the intima in elastic arteries was observed in a fetus of 26 weeks' gestation. Pronounced obliterative intimal changes were found in only one subject, an 11-year-old girl with severe pulmonary hypertension.

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The Pulmonary Arterial Tree in Ventricular Septal Defect

A Quantitative Study of Anatomic Features in Fetuses, Infants, and Children

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With the technical assistance of Noeke Wagenvoort

THE SIGNIFICANCE of the changes that occur in the pulmonary vascular tree in congenital heart disease with pulmonary hypertension is far from being fully understood. Data obtained from systematic investigations of the anatomic changes in young persons are exceedingly rare. For better insight into the origin of such lesions and in order to determine the sequence of events during their development, a study of the pulmonary arteries in young children with ventricular septal defect was considered of importance. By studying the pulmonary arteries in cases of ventricular septal defect in an age group ranging from fetal life to 12 years, it was hoped to obtain information regarding the early development of such lesions as medial hypertrophy, intimal proliferation, and plexiform or glomerulus-like structures.

Medial hypertrophy is usually judged from the thickness of the media as compared with the diameter of the vessel. As has been pointed out,[1] this method alone is inadequate for establishing the degree of, or even the presence of, hypertrophy, since constriction and dilatation will influence the relative thickness of the media without affecting the amount of vascular muscle tissue. Therefore it was also the aim in this study to establish the ratio of medial tissue to pulmonary parenchyma, as an index of the absolute amount of medial muscular tissue. By use of both methods, a more comprehensive understanding can be formed regarding the degree of medial hypertrophy or atrophy, vasoconstriction or vasodilatation.

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Material and Methods

The material for this study was taken from 50 cases of ventricular septal defect, uncomplicated by other congenital cardiac lesions, in fetuses, infants, and children coming to necropsy in the Section of Pathology of the Mayo Clinic. Of these 50 subjects, 25 were less than 1 year of age, ranging from 26 weeks of fetal life to 11 months of postnatal life, and 25 were 1 year to 12 years old (table 1). There were 31 males and 19 females. In 32 cases the subjects died after operation for their cardiac malformation. In six cases from the nonsurgical group (cases 6, 11, 12, 14, 15, and 19) the cause of death was considered to be chronic heart failure due to the congenital cardiac lesions. The other 12 subjects died from causes unrelated to the cardiac condition, as follows: prematurity (cases 1, 2, and 3), placenta previa (case 4), noncardiac congenital malformations (cases 5, 7, 8, 9, 10, and 13), amyotonia congenita (case 28), and acute pericarditis (case 49). Clinical data were available for all subjects, and hemodynamic data obtained by cardiac catheterization were available for 26 of the 50 cases (table 1).

Only the right lung was used for the histologic study of the pulmonary vessels. Blocks were taken from five segments as follows: (1) apical and (2) pectoral segments of the upper lobe, (3) middle lobe, and (4) apical and (5) anterobasal segments of the lower lobe. The blocks were embedded in paraffin, and sections were cut at 6 microns. One section from each block was stained with hematoxylin and eosin and one with Lawson's elastic stain, counterstained with van Gieson's connective-tissue stain. Sections stained by the latter method were used for the quantitative studies of the media, and those stained by the hematoxylin and eosin technic were helpful in the evaluation of lesions other than changes in medial thickness.

The sections were mixed with sections from cases of atrial septal defect and aortic atresia from two other studies in progress. Neither the cardiac condition nor the age of the patient was known to the investigators until all measurements and calculations were completed.

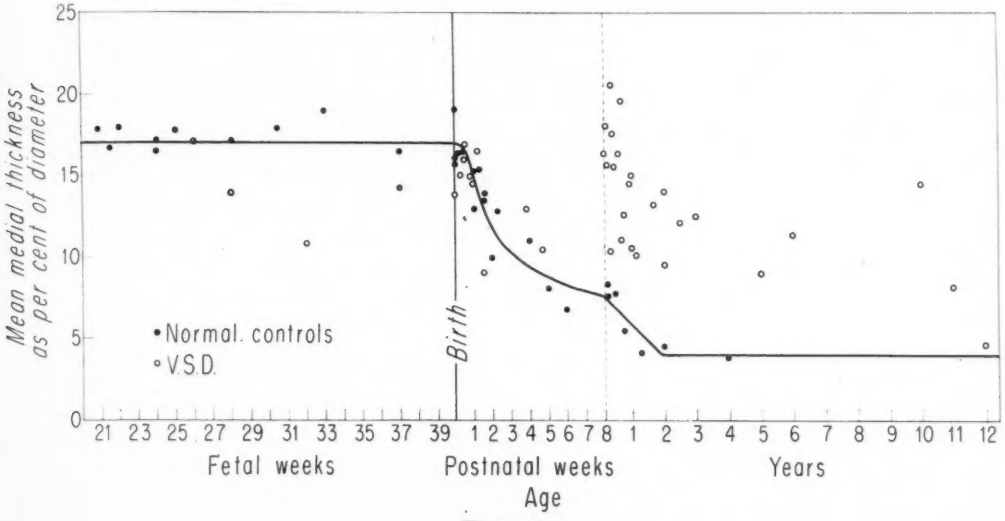

Figure 1

Mean medial thickness expressed as percentage of diameter in 38 cases of ventricular septal defect in fetuses, infants, and children as compared with that in controls of corresponding age. Solid curve is a composite expression of the individual control values.

Twelve cases in which intimal proliferation was pronounced to severe were excluded from the quantitative study, since pronounced thickening of the intima and eventual obliteration may lead to secondary atrophy of the medial muscular tissue in a long segment of the affected branch. In the remaining 38 cases intimal changes, if present at all, were mild or moderate.

The method used for the quantitative study of medial hypertrophy has been described in detail elsewhere[1] and is summarized here. The media and external diameter of 20 consecutive muscular pulmonary arterial branches, regardless of size, were measured in each of the five segments of lung. In this way 100 arteries were measured per lung, or 3,800 arteries in all the cases in which quantitative studies were made. The arteries were unselected except for the requirement that a virtually circular cross section be present in the sections to permit measurement. The medial thickness of each artery was expressed as a percentage of the external diameter (relative medial thickness).

In order to determine the ratio of medial tissue to pulmonary parenchyma, both the average medial cross-sectional area and the number of muscular pulmonary arteries per unit of lung tissue had to be known. The cross-sectional area of the media in each artery was calculated. The surface area of pulmonary parenchyma in the sections was measured by planimetry. Since the total area of the parenchyma per lung generally averaged 7.5 cm.^{2}, it was impractical to count all the small arterioles in such a large area. Therefore, the arteries were divided into large and small arteries. All large vessels were counted in the sections from each subject regardless of the plane of section. The number of the small arteries could be derived from this figure, since the ratio of large to small vessels was known from the measurements of the 100 arteries per lung. The dividing line between a small artery and a large artery for a given case was arbitrarily fixed at 40, 50, or 70 microns of external diameter, the value chosen depending on which one would provide a comparatively constant ratio between both groups.

When the average medial cross-sectional area and the number of arteries per square centimeter of pulmonary parenchyma were known for both large and small arteries, the medial cross-sectional area per square centimeter of parenchyma could be calculated. This ratio of medial to pulmonary tissue was expressed as an index, hereafter referred to as the index of medial surface area. (The actual cross-sectional area of arterial medial tissue in square microns per square centimeter of pulmonary parenchyma can be obtained by multiplying the index by 100 π.)

The relative medial thickness and the index of medial surface area in the study cases were compared with corresponding values found in a series of fetuses, infants, and children with normal hearts and lungs[3] and with those found in older

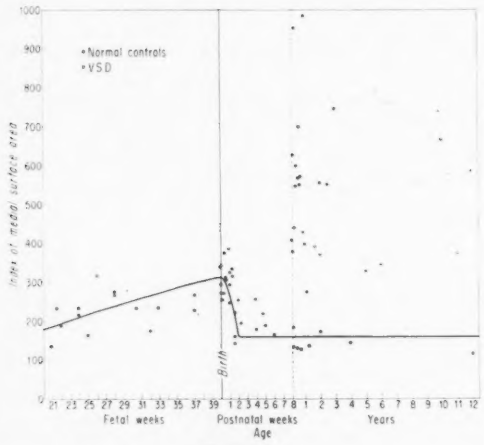

Figure 2

Index of medial surface area in 38 cases of ventricular septal defect in fetuses, infants, and children as compared with that in controls of corresponding age. Solid curve is a composite expression of the individual control values.

children and adults[1] from two previous studies. Other pulmonary vascular lesions, such as intimal proliferation, thrombi, and plexiform or glomerulus-like structures, were studied when present in the material in all 50 cases. An attempt was made to correlate pathologic findings with clinical and hemodynamic data and with the size of the ventricular septal defect.

Results

The available data are summarized in table 1. The mean medial thickness in the 38 cases in which measurements were made is shown also in figure 1, where the values are compared with those obtained from a control group previously reported.[3] The index of medial surface area is compared with the corresponding results in the control group in figure 2.

The deviation from the normal of the values derived from the group with ventricular septal defect differed greatly with age. During fetal and early postnatal life, both the mean medial thickness and the index of medial surface area were not far from normal limits (fig. 3*a*). It is striking, however, that in several subjects who died in the neonatal period, the mean relative medial thickness was somewhat less than that in the controls. It appeared that in these cases a certain number of pulmonary arterial branches had a thin media as compared with that in normal subjects at comparable ages (fig. 3*b*). These vessels, some of which had lost virtually all muscular tissue, were responsible for the low average of the thickness of the medial layer.

Some increase in medial thickness and in the absolute amount of medial tissue appeared to be present in the two subjects aged 28 and 33 days; an increase was certainly present after that age. From 8 weeks onward, both the thickness and the index of surface area were usually far greater than those in the control group (fig. 3*c*). Extreme medial hypertrophy was observed in patients as young as 3 and 4½ months of age. Only in one case, that of a 12-year-old child (case 49), were the pulmonary arterial branches within normal limits with regard to medial thickness and index of medial surface area.

Although there was occasionally an appreciable difference in medial thickness in the segments of the same lung, these differences were not characteristic for a certain segment. When all cases were taken into account, no concentration of vessels of a certain thickness in one location in the lung was found.

Medial hypertrophy was considered present in all 12 cases in which no measurements were made. Although it would have been hazardous to attempt to evaluate the degree of hypertrophy by quantitation because of the presence of severe intimal changes that might have affected the medial thickness and index of medial surface area, it was obvious that medial hypertrophy was present. It was particularly evident in the large muscular arteries. Small arteries may exhibit a relatively thin media when occluded by intimal proliferation, including a portion of the vessel distal to the occlusion. This may account for the finding of Rosenberg and associates[4] that in some cases of intimal proliferation the media was of normal thickness. In the present series elastosis of the media was found frequently in several subjects in the older age group.

On the whole, intimal thickening was an exceptional finding below the age of 1 year;

Table 1

Data in Fifty Cases of Ventricular Septal Defect in Fetuses, Infants, and Children

Case	Age	Sex	Medial thickness, per cent of diameter (in 38 cases)	Index of medial surface area (in 38 cases)	Intimal	Frequency of plexiform lesions	Size of ventricular septal defect*	Pressure in pulmonary artery or right ventricle†
1	26 fetal wk.	M	17.1	317	—	—	S	
2	28 fetal wk.	M	13.9	268	—	—	L	
3	32 fetal wk.	F	10.8	174	—	—	S	
4	Stillborn	M	13.8	342	—	—	S	
5	2 da.	M	15.0	272	—	—	L	
6	3 da.	M	16.0	312	—	—	S	
7	4 da.	F	16.9	306	—	—	L	
8	6 da.	F	14.9	387	—	—	L	
9	7 da.	F	14.5	325	—	—	L	
10	9 da.	F	16.5	316	—	—	L	
11	11 da.	F	9.1	222	Slight	—	L	
12	27 da.	F	12.9	257	Moderate	—	L	
13	33 da.	F	10.4	219	—	—	L	
14	8 wk.	M	16.3	408	—	—	L	
15	10 wk.	M	18.1	380	—	—	L	
16	3 mo.	M	15.7	627	Slight	—	L	90/51
17	4 mo.	M	10.3	440	—	—	L	43/4‡
18	4½ mo.	M	20.6	953	—	—	L	70/3‡
19	5 mo.	M	17.6	548	—	—	L	
20	5½ mo.	M	15.5	600	—	—	L	
21	7 mo.	M	16.3	568	—	—	L	60/31
22	8 mo.	M	11.0	551	Slight	—	S	58/21
23	8 mo.	M	19.6	700	Slight	—	L	57/15
24	9 mo.	F	12.6	572	—	—	S	76/5‡
25	11 mo.	M	14.5	429	—	—	L	66/2‡
26	1 yr.	M	15.0	985	—	—	L	84/49
27	1 yr.	M	10.5	399	—	—	L	
28	13½ mo.	F	10.1	277	—	—	S	
29	20 mo.	F	13.2	392	Moderate	—	S	
30	2 yr.	M	14.0	557	Moderate	—	S	66/22
31	2 yr.	M	9.5	372	—	—	S	75/10‡
32	2½ yr.	M	—	—	Severe	—	L	82/32
33	2½ yr	M	12.1	552	Slight	—	L	60/9‡
34	2½ yr.	M	—	—	Severe	Occasional	L	72/41
35	3 yr.	F	12.5	745	Slight	—	L	75/45
36	3½ yr.	M	—	—	Severe	Occasional	L	94/44
37	3½ yr.	M	—	—	Pronounced	—	L	100/—‡
38	4 yr.	M	—	—	Severe	Occasional	L	112/3‡
39	5 yr.	M	9.0	330	Slight	—	S	42/10‡
40	6 yr.	F	11.3	347	Slight	—	L	85/47
41	6 yr.	F	—	—	Severe	Numerous	L	
42	6 yr.	M	—	—	Pronounced	—	L	
43	6 yr.	F	—	—	Severe	Scarce	L	57/18
44	8 yr.	M	—	—	Pronounced	—	L	
45	8 yr.	F	—	—	Pronounced	—	L	58/2‡
46	10 yr.	F	14.4	667	Slight	—	L	83/48
47	10 yr.	F	—	—	Pronounced	Scarce	L	87/2‡
48	11 yr.	F	8.2	374	Moderate	Scarce	L	97/46
49	12 yr.	M	4.6	114	Slight	—	S	
50	12 yr.	M	—	—	Severe	—	L	116/66

*The size of the ventricular septal defect was compared with the body surface area. The defect was considered large (L) when its surface area was 1 cm.^{2} or more per square meter of body surface area, and it was termed small (S) when its area was less than this amount.^{2}

†The cardiac catheterization data were collected by Dr. Earl H. Wood and colleagues, aided by research grant H-3532 from the United States Public Health Service.

‡Pressures in right ventricle.

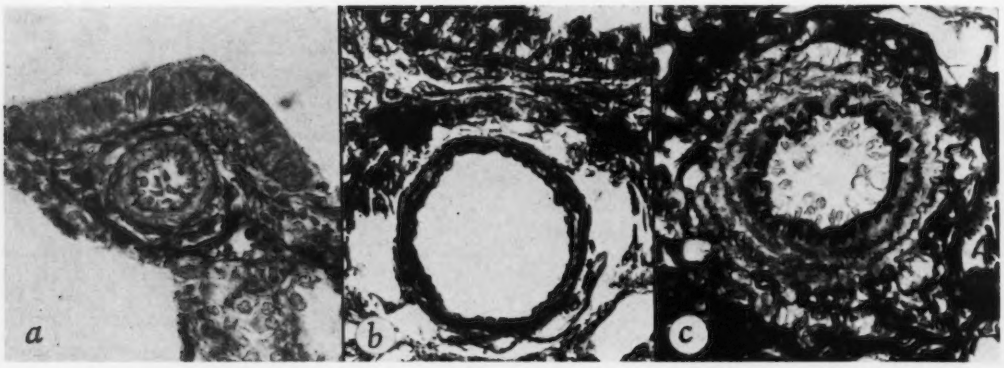

Figure 3

a. Pulmonary arterial branch in a 2-day-old infant with ventricular septal defect. Vessel is thick-walled but not different from average normal pulmonary arterial branch in newborn period (elastic stain). b. *Pulmonary arterial branch in a fetus of 32 weeks' gestation with ventricular septal defect. Media is thin and lumen wide as compared with those in most cases of ventricular septal defect and in normal subjects (elastic stain).* c. *Muscular pulmonary arterial branch with pronounced medial thickness and some elastosis, in a 7-month-old child with ventricular septal defect (elastic stain).*

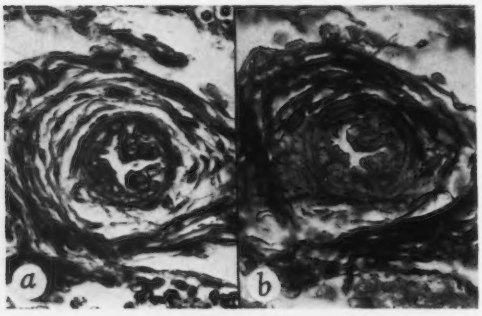

Figure 4

Pulmonary arterial branch in a fetus of 28 weeks' gestation with ventricular septal defect. Bundles of muscle fibers are seen in intima (a. hematoxylin and eosin, b. *elastic stain).*

from then on it was the rule (table 1). In two cases, those of a fetus of 28 weeks' gestation and an 11-day-old infant, some pulmonary arterial branches showed bundles of longitudinal muscle fibers in the intima (fig. 4). The 11-day-old infant was also the youngest subject in whom at least a slight degree of intimal proliferation—that is, increase of the intimal connective tissue—was occasionally observed. A 27-day-old infant was the only subject in the age group younger than 1 year in whom intimal proliferation gave rise to an appreciable degree of narrowing of the lumen (fig. 5). In the age period from 1 year to 12 years all but a few subjects had some degree of intimal thickening. Glomerulus-like structures were present in only seven of these cases.

Occasionally the intimal thickening was of the cellular type (fig. 5). This was especially true in the younger children. In some cases the intimal proliferation gave rise to a thin strand of connective-tissue cells that crossed the lumen as a septum (fig. 6*a*).

Sometimes the intimal proliferation was formed by a relatively thin layer of hyaline material (fig. 6*b*). The most common form of intimal thickening, which might have been the final stage of the other types, was a concentric proliferation that often gave rise to severe narrowing or even occlusion of the vessel. At the same time, the media of these vessels was relatively thin and appeared stretched (fig. 7). This type of lesion was confined to subjects in the age group older than 1 year. Most forms of intimal thickening were particularly pronounced in the proximal segment of an arterial branch after its ramification. Occasionally the proliferation had spread to the main vessel as a patch around the orifice of the branch.

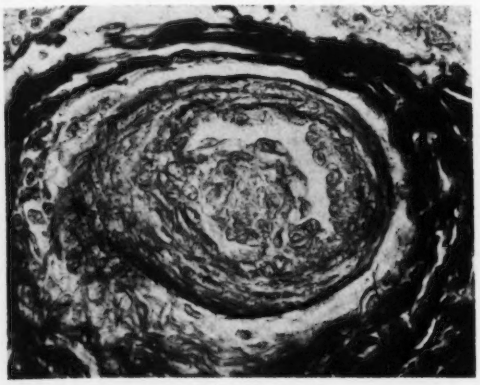

Figure 5

Cellular intimal proliferation in pulmonary arterial branch of a 27-day-old infant with ventricular septal defect (elastic stain).

The plexiform or glomerulus-like structures were confined to the older subjects and were not observed in subjects less than 2½ years old. In some cases these structures were extremely numerous (fig. 8).

Discussion

During fetal life a ventricular septal defect is unlikely to cause hemodynamic disturbances. Pulmonary resistance is high in the fetus, and the pulmonary flow consequently is low.[5] Normally, a communication between the systemic and the pulmonary circulation is provided by the patent ductus arteriosus. A defect in the ventricular septum adds to this communication without any appreciable change in hemodynamics. At birth, expansion of the normal fetal lung is associated with a considerable fall of resistance and a drop in pulmonary pressure.

In normal fetuses the thickness of the media remains constant, whereas the index of medial surface area shows a gradual increase until the time of birth. After birth there is a rather sudden drop in thickness and in the index of surface area over a period of approximately 10 to 14 days.[3] This is also demonstrated in figures 1 and 2.

In cases of ventricular septal defect generally, no pronounced deviation from the normal occurred in this early age period. In two of the three fetuses (cases 2 and 3), in a

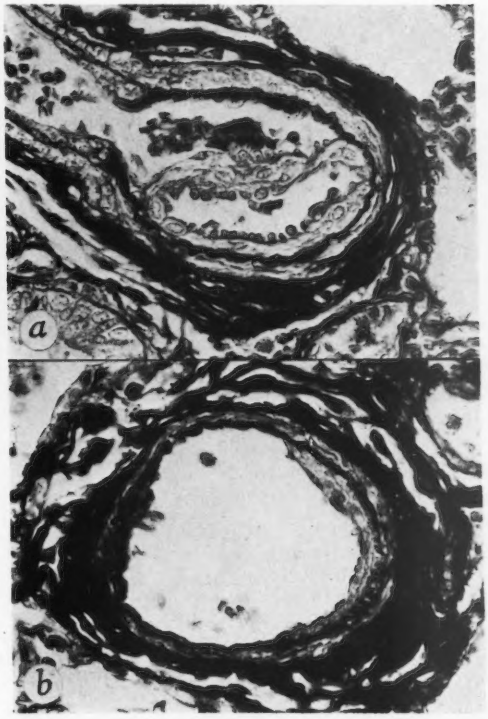

Figure 6

a. *Cellular intimal proliferation forming septum and partitioning lumen in pulmonary arterial branch of a 5-year-old child with ventricular septal defect (elastic stain).* b. *Thin layer of mostly hyaline intimal proliferation in a 5-year-old child with ventricular septal defect (elastic stain).*

stillborn infant (case 4), and in an 11-day-old infant (case 11), the medial thickness was below normal (fig. 3*b*). A similar finding was noted by Heath and associates[6] in two cases of patent ductus arteriosus and by Wagenvoort and Edwards[7] in a case of aortic atresia. These findings may represent underdevelopment of the pulmonary arterial walls, as in case 3, in which the index of medial surface area was certainly lower than normal and in which several arteries lost every trace of muscular tissue. In three of these four cases, however, the index of medial surface area was normal, and therefore the thin pulmonary arterial media was rather indicative of vasodilatation, whatever the cause of this might have been.

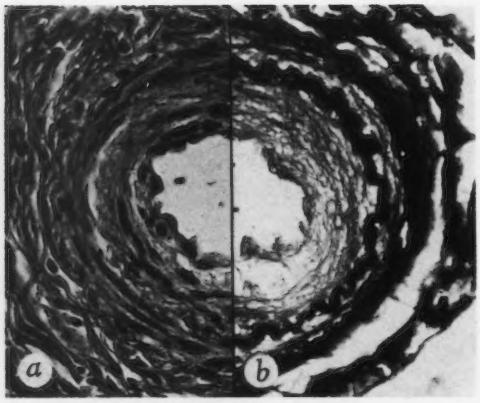

Figure 7

Concentric intimal proliferation in pulmonary arterial branch of a 1-year-old child with ventricular septal defect (a. hematoxylin and eosin, b. elastic stain).

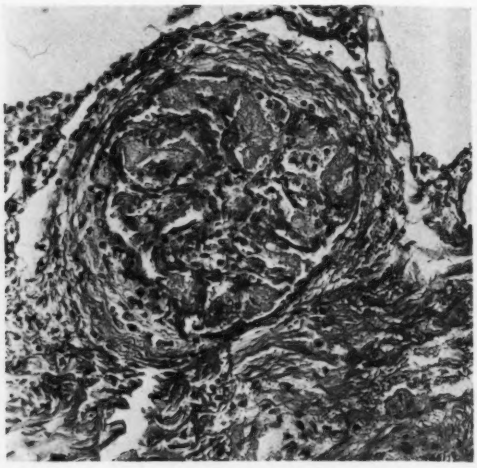

Figure 8

Plexiform or glomerulus-like structure in a 3-year-old child with ventricular septal defect. Lesion is lying in a branch shortly beyond its origin from a larger artery. Recent thrombosis of channels in lesion is present (hematoxylin and eosin).

Although both the medial thickness and the index of medial surface area were apparently normal in infants with ventricular septal defect, both of these values tended to decrease soon after birth. The limited number of our cases in the critical period of the second and third weeks of life makes it difficult to ascertain whether this decrease was just as pronounced as it is in normal persons. It might be that the lower limit of normal medial thickness and of the normal index is never reached. Soon after the second or third week of life the pulmonary arteries in patients with ventricular septal defect showed an increase in thickness as well as in the index of medial surface area, in contrast to what is found in normal lungs (figs. 1 and 2). From that time on, medial hypertrophy was certainly present. In the two children aged 27 and 33 days, this increase might still have been questionable. From 8 weeks onward, however, the increase was obvious, and in children as young as 3 and 4 months the media was often extremely hypertrophic.

The decrease in medial thickness and in the index of medial surface area in the age period of 2 to 5 weeks after birth may correspond with phase I (plethoric lungs) of the clinical picture in large ventricular septal defects described by Dammann and Ferencz.[8] Since this clinical phase usually lasts up to 2 years, it is difficult to carry the comparison between the clinical picture and the structural changes beyond the fifth week; our material shows thickening of the media after that period. This change would suggest an increased resistance to flow. Since the clinical picture does not reflect this, it may be that the hypertrophic arteries are capable of vasodilatation and thus exercise less resistance to flow than might be supposed from the cross-sectional histologic appearance.

Whether there is an actual persistence of the fetal type of pulmonary arterial tree[9] or whether the hypertrophic state of the vessels is reached after a short interval in which the vessels are normal or near normal is difficult to answer from this limited material. The material reported is selected in that all subjects died, most of them as a result of their cardiac malformation. Therefore, it is possible that the findings in this group do not fully reflect the structure of the pulmonary vascular tree in persons with ventricular septal defect who survive.

Although intimal proliferation apparently occurs later than medial hypertrophy, it occasionally may be found in very young children. The first slight evidence of intimal thickening was observed in a child 11 days of age (case 11), and moderate proliferation occurred as early as 27 days (fig. 5). However, these are exceptions. Again, even considering the common occurrence of a pronounced degree of intimal proliferation from the age of 20 months onward, it must be emphasized that almost all subjects in this later age group were operated on for their cardiac condition and that they therefore represent a selected group in which relatively severe lesions of the pulmonary vessels were to be expected.

The same is true for the glomerulus-like structures (fig. 8). These complex lesions develop as a result of longstanding and severe pulmonary hypertension.[10, 11] It is not surprising, therefore, that they appeared at an even later stage than intimal proliferation. The youngest subject in this series in whom glomerulus-like structures were found was 2½ years of age.

Comparison of the clinical data with the histologic findings in the pulmonary arterial tree, although extremely important, has its limitations. As pointed out, this type of pathologic study involves a selection of cases. One could get around this problem by using biopsies, if available, but biopsy material is inadequate for quantitative analysis because of its limited quantity. Only if we could confine our study to patients who died from causes unrelated to their cardiac condition could we claim that our material more or less reflected the natural history of the pulmonary circulation in ventricular septal defect. Such cases are scarce, however, and rarely provide enough material to permit the drawing of conclusions.

In the postnatal period, eight of the subjects in this series were considered to have died from causes other than congenital cardiac disease. Only one of these (case 28) showed moderate medial hypertrophy, although it was less than that of any of the subjects who died as a result of cardiac failure or after cardiac operation. The other seven had only questionable hypertrophy of the media or none at all. Intimal proliferation did not occur in these eight subjects, except for slight thickening of the intima in case 49.

It could be expected that the septal defect in patients who died from causes unrelated to their cardiac condition would be smaller in relation to their body surface area than in patients who died from cardiac failure or after cardiac operation. This was certainly true for the two oldest children (cases 28 and 49) but less obvious for the others in this group.

Six patients from the nonsurgical group were thought to have died from cardiac failure due to their congenital heart disease. All six were young children. Only the three oldest of this series, aged 8 and 10 weeks and 5 months (cases 14, 15, and 19), had pronounced medial hypertrophy. In two others (cases 11 and 12) slight and moderate intimal proliferation, respectively, were observed. The size of the ventricular septal defect per square meter of body surface area in this group was 2 cm.^{2} or more.

Summary

A quantitative analysis was made of the pulmonary arterial medial thickness and index of medial surface area (ratio of medial tissue to pulmonary parenchyma) in 50 cases of uncomplicated ventricular septal defect in fetuses, infants, and children. The ages of the subjects ranged from 26 weeks of fetal life to 12 years. The results were compared with those obtained from a control group of the same age.

During the fetal and newborn period, both the thickness and the index of surface area of the media were generally within normal limits, although in an occasional case pulmonary arterial branches were considerably thinner than those in corresponding controls. The subjects between 1 week and 5 weeks of age had a medial thickness and an index of medial surface area that were lower than the average

values at the time of birth. In this regard the pulmonary arterial tree in cases of ventricular septal defect corresponded with that in normal newborn infants. Soon after, however, and most clearly from 8 weeks on, the subjects with ventricular septal defect showed a pronounced rise both in medial thickness and in the index of medial surface area, indicating the presence of considerable medial hypertrophy.

Although intimal proliferation was observed in two infants of 11 and 27 days of age, it was uncommon in children less than the age of 1 year. Above that age it was almost invariably present. Plexiform or glomerulus-like structures were found in seven cases. The youngest patient with these lesions was 2½ years of age.

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Religio Medici

That there was a Deluge once, seems not to me so great a Miracle, as that there is not one always.—SIR THOMAS BROWNE. *Religio Medici*, 1642, Edited by W.A. Greenhill, M.D., Oxon., London, MacMillan and Co., Limited, 1950, p. 39.

Blood Volume Changes in Cyanotic Congenital Heart Disease and Polycythemia Rubra Vera

By DAVID VÉREL, M.D.

IT IS WELL KNOWN that in polycythemia rubra vera the total blood volume increases as the hematocrit level rises beyond approximately 55 per cent.[1-2] This increase masks the extent of the polycythemia and insures that the plasma volume is not greatly diminished despite an increase in red cell volume to twice or three times the normal value. The changes in adults suffering from cyanotic congenital heart disease have not been precisely defined. It is less easy to compare the blood volume in this condition with expected normal values because the limits of the normal blood volume are poorly defined by reference to height or weight.[3] Statistically valid limits of blood volume have been determined in adult subjects by means of height, weight, girth, and fat thickness.[3] In this paper patients of adult stature suffering from polycythemia rubra vera and from congenital heart disease are compared with normal adults.

Methods

Red cell volume was measured with radioactive phosphorus^{32} or radioactive chromium^{51}-labeled red cells by a modification of the methods of Reeve and Veall[4] and of Mollison and Veall.[5] Approximately 10 ml. of red cells were withdrawn with sterile precautions and placed in a sterile stoppered ampoule. The red cells were centrifuged, and the supernatant plasma was added to 100 ml. of sterile ice-cold normal saline. Three milliliters of isotonic acid-citrate-dextrose mixture were added to the red cells and to this approximately 15 microcuries of radioactive phosphorus^{32} or 50 microcuries of radioactive chromium^{51} were added. The cells were then incubated for 30 minutes at 37°, if phosphorus was used, and at room temperature, if chromium was used. The cells were then washed three times with cold saline-plasma mixture. An accurately measured volume of 20 ml. was then injected into the patient intravenously and two samples were taken at 10-minute intervals. Suitable standards were prepared and the radioactivity of the samples, the standards, and the saline in which the cells were suspended were counted in a Type N 550 Ekco* well-type scintillation counter for the chromium and a standard liquid-type Geiger-Müller tube for the phosphorus.

Plasma volume was measured in a few patients in each group with either Evans blue radioactive iodine^{131}, labeled albumin, or high molecular weight dextran.[6] In other cases the plasma volume was calculated from the red cell volume with use of a body venous hematocrit ratio of 0.92 for patients in whom the hematocrit value was below 60 per cent. In those exceeding 60 per cent a body venous hematocrit ratio of 0.94 was employed, since this gave a more precise estimate.[7, 8] The hematocrit value was estimated in duplicate on all samples by spinning in 10-cm. Wintrobe tubes in a centrifuge at 15-cm. radius for 55 minutes at 3,000 r.p.m. The hematocrit values were corrected for plasma by the method of Chaplin and Mollison.[9] Height, weight, and girth were measured by standard methods, fat thickness was measured below the angle of the scapula with a caliper. Blood volume was predicted from these measurements by the formula of Hicks et al.[3]

Results

Blood volume measurements were made on 12 patients with congenital heart disease. Their ages ranged from 16 to 46 years, the venous hematocrit values from 44.0 to 83.2 per cent, and the red cell volume from 1,890 to 5,170 ml. The calculated blood volumes ranged from 3,940 to 8,000 ml. (table 1).

Similar measurements were made on 12 patients with polycythemia rubra vera who had not been subjected to venesection. Their ages ranged from 38 to 66, the venous hematocrit values from 50.0 to 68.8 per cent, and the red cell volume from 2,550 to 6,460 ml. The calculated blood volume ranged from 4,800 to 9,400 ml. (table 2).

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*Ekco Electronics Ltd. Southend-on Sea, Essex, England.

Table 1

Blood Volume Data in Congenital Heart Disease

Case no.	Diagnosis	Measured values				Predicted values				Per cent of normal value		
		Age	Red cell volume	Plasma volume	Blood volume	Venous hematocrit	Red cell volume	Plasma volume	Blood volume	Red cell volume	Plasma volume	Blood volume
		yr.	ml.	ml.	ml.	%	ml.	ml.	ml.	%	%	%
1	Eisenmenger	20	1890	2560	4450	46.5	2070	2855	4925	91	90	90
2	Fallot	24	5170	2830	8000	68.5	2510	3480	5990	206	81	134
3	Eisenmenger	29	2110	2390	4500	50.0	2000	2790	4790	105	86	94
4	Eisenmenger	43	2910	2670	5580	56.6	2260	3110	5370	129	86	104
5	Fallot	44	3230	1000	4230	83.2	1740	2400	4140	186	42	102
6	Patent ductus arteriosus and reversed shunt	46	4000	1670	5670	78.0	2340	3230	5570	171	52	102
7	Transposition	16	4740	1860	6000	78.0	2130	2940	5070	223	63	130
8	Eisenmenger	24	2000	2940	4940	44.0	2190	3030	5220	91	97	95
9	Eisenmenger	17	2000	2520	4520	49.0	2080	2870	4950	96	85	91
10	Eisenmenger	29	2340	2210	4550	54.7	1900	2610	4510	123	85	101
11	Patent ductus and reversed shunt	21	2980	2440	5420	58.5	2000	2755	4755	149	89	113
12	Eisenmenger	35	2310	1630	3940	62.4	1630	2240	3870	142	73	102

Table 2

Blood Volume Data in Polycythemia Rubra Vera

Case no.	Age	Measured values				Predicted values			Per cent of normal value		
		Red cell volume	Plasma volume	Blood volume	Venous hematocrit	Red cell volume	Plasma volume	Blood volume	Red cell volume	Plasma volume	Blood volume
	yr.	ml.	ml.	ml.	%	ml.	ml.	ml.	%	%	%
1	57	3310	2060	5370	67.0	1640	2260	3900	202	91	138
2	43	3410	2890	6300	50.0	2210	3040	5250	154	95	120
3	54	4830	3060	7890	68.8	1750	2420	4170	276	126	190
4	66	3750	2850	6600	60.5	2600	3580	6180	144	80	107
5	63	4550	2810	7360	67.3	2020	2800	4820	226	100	153
6	51	6460	2940	9400	74.5	2670	3680	6350	244	80	148
7	50	4640	2600	7420	70.0	2600	3360	5960	179	77	122
8	38	3880	2140	6020	68.7	1800	2490	4290	216	86	140
9	46	5480	2130	8610	68.8	2840	3560	6300	193	88	137
10	51	4170	2860	7030	64.1	2200	3040	5240	190	94	134
11	45	2550	2250	4800	54.4	2120	2980	5700	120	75	94
12	43	3450	2380	5800	64.5	1810	2490	4300	190	96	134

The body measurements in the two groups were comparable. The blood volume and red cell volume predicted from these body measurements are shown for each patient. In each case the estimation of blood volume has a standard deviation of 383 ml.[3]

The red cell volumes, venous hematocrit values, and body builds in these two groups are comparable with each other and may be compared with the data of the normal subjects published by Hicks et al.[3] It is therefore possible to use a predicted normal value for each patient obtained from the body measurements as a basis of comparison. The age of the patients was not found to have a measurable effect in determining blood volume,[3] so that the difference between the two groups of patients does not invalidate their comparison. For the purposes of comparison the data are most conveniently expressed as a ratio of the

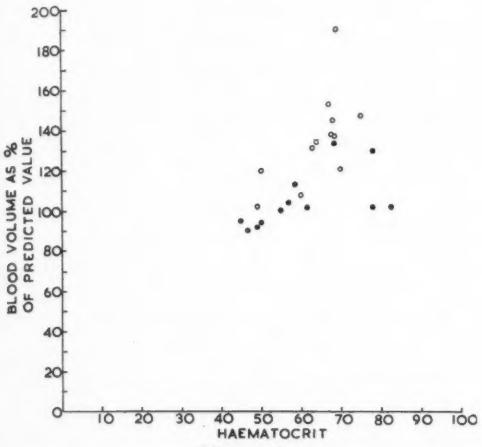

Figure 1

Blood volume expressed as a percentage of the predicted normal value related to the venous hematocrit. Dots, *cyanotic congenital heart disease;* circles, *polycythemia vera.*

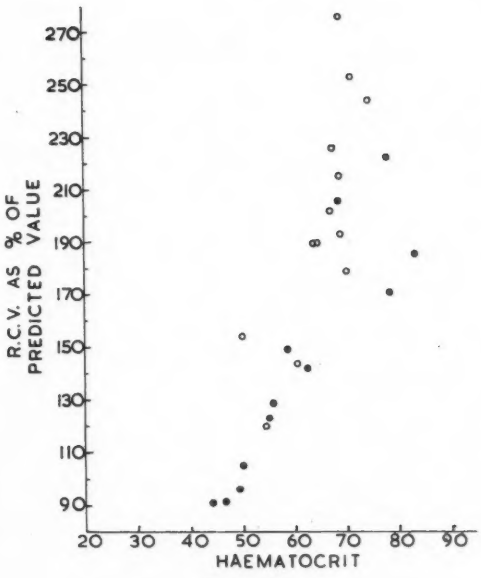

Figure 2

Red cell volume expressed as a percentage of the predicted normal value related to venous hematocrit. Dots, *cyanotic congenital heart disease;* circles, *polycythemia rubra vera.*

function measured to the predicted normal value. Throughout, this ratio has been expressed as a percentage of the normal value (tables 1 and 2).

Discussion

Measurements of blood volume in congenital cyanotic heart disease have been reported by Cassels and Morse (1947)[10] and by Hallock (1940).[11] Both found a variable increase in the total blood volume due to a rise in the red cell volume, the plasma volume being usually diminished. Cassels and Morse[10] suggested that abnormal circulation in congenital heart disease required an elevation of circulating blood volume, the addition to the normal quantity being due to the volume shunted in one direction or the other through an abnormal communication. The observations reported in this paper do not support this view.

When the total blood volume in the patients reported here is expressed as a percentage of normal and related to the venous hematocrit level, it is clear that in congenital heart disease the total blood volume may remain within normal limits up to a hematocrit level of over 80 per cent (fig. 1). Only in two cases (nos. 2 and 7) did the total blood volume rise significantly above the predicted normal value; in both cases the red cell volume itself had risen close to the predicted normal volume, so that an increase of blood volume was inevitable if the plasma volume was to be retained. In the remaining patients the increase in red cell volume was not so gross. A similar tendency may be observed in the patients reported by Cassels and Morse[10] and by Holman.[11] In all three patients reported by Cassels and Morse the total blood volume exceeded the predicted normal volume by more than 100 per cent and the total red cell volume itself was considerably above the predicted normal blood volume. It seems likely therefore that the increases in blood volume reported previously and in this paper are not related to the quantity of blood shunted but rather to the degree of polycythemia. This response differs from that found in the patients with polycythemia rubra vera in whom the rapid increase in total blood volume is found as the hematocrit level rises above 55

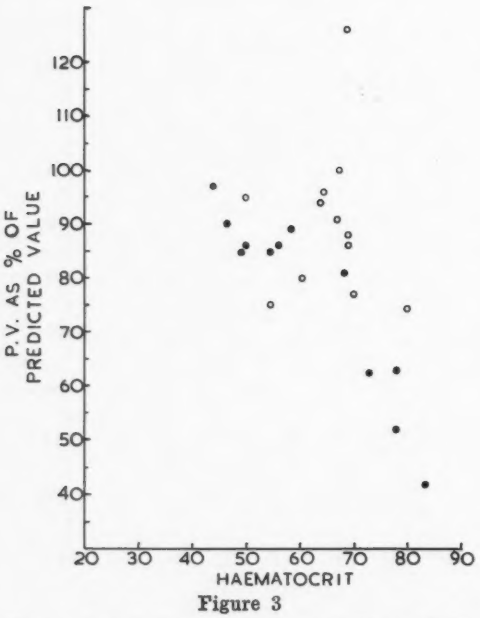

Figure 3

Plasma volume expressed as a percentage of the predicted normal value related to venous hematocrit. Dots, *cyanotic congenital heart disease;* circles, *polycythemia rubra vera.*

per cent. This confirms the well-known observations of Gibson and Evans.[1]

When the changes in the red cell volume found in polycythemia rubra vera and congenital heart disease are compared (fig. 2), it is seen that at any hematocrit level the red cell volume in polycythemia rubra vera is higher than that in congenital heart disease. This is a simple result of the increase in total blood volume seen in polycythemia rubra vera, which conceals the true extent of the polycythemia.

The changes in plasma volume expressed as percentages of the predicted normal volume are shown in figure 3. In polycythemia rubra vera there is no very consistent change in plasma volume, which ranges between 75 and 126 per cent of normal, although, as might be expected, the majority of plasma volume measurements are below normal. In congenital heart disease the response is quite different. A remarkably consistent fall in plasma volume occurs as hematocrit values rise,

Table 3

Comparison of the Plasma Volume

Case no.	Calculated* plasma volume ml.	Measured plasma volume ml.	Difference ml.
1	2885	2560	+ 325
2	2830	2390	+ 440
3	2390	2510	− 120
4	2670	2560	+ 110
5	1240	1000	+ 240
6	1870	1670	+ 200
7	1700	1860	− 160
8	2940	2940	± 0
9	2610	2520	+ 90
10	2210	2210	± 0
11	2210	2440	− 230
12	1695	1630	+ 65

*Calculated from the formula P.V. = predicted B.V. x 58/100 (147.5—1.15 Ht).

until the hematocrit is about 80 per cent when the plasma volume is about half its normal value or less. The correlation coefficient is significant ($r=-0.920$). These data can be used to calculate with a fair degree of confidence the plasma volume in subjects suffering from congenital heart disease. The regression equation derived from the data is $\%PV=-1.15\ (\%Ht)\ +147.5$. If the normal blood volume is calculated by the data of Hicks et al.[3], the plasma volume may therefore be inferred from the formula $PV=BV \times 58/100 \times K$, in which $K=(147.5-1.15\ (\%Ht))$. The correlation between the measured and predicted plasma volumes is shown in table 3.

These observations may be important in the surgery of congenital heart disease. The figures in table 3 indicate that in subjects of adult stature the plasma volume may be as low as 1 liter when a plasma volume of 2.4 liters might be expected. In such patients less than half the normal quantity of fibrinogen circulates in the blood and the total available quantities of platelets and prothrombin are comparably reduced. These changes may well be involved in the hemolytic tendency reported in certain patients with congenital heart disease following surgery. It is clear that further research is indicated into the changes occurring during readjustment from this abnormal status after surgery.

Summary

The blood volume has been measured in 12 adult patients with cyanotic congenital heart disease and in 12 patients with polycythemia rubra vera by radioactive isotopes. In congenital heart disease the total blood volume was found to be within normal limits provided the red cell volume had not risen so high as to make an increase in total blood volume inevitable. In polycythemia rubra vera the total blood volume increased rapidly once a hematocrit level of 55 per cent had been exceeded. Increasing polycythemia in congenital heart disease was found to be associated with the predictable fall in plasma volume, and a formula for estimating the plasma volume from the predicted normal blood volume and the hematocrit is presented. It is suggested that the low plasma volume that may be found in very polycythemic patients may be partly responsible for their known tendency to postoperative hemorrhage.

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Obstacles encountered in research, however, sometimes yield quite as important results as those which were anticipated. In 1897, when I was using the recently discovered X-rays in studying the movements of the stomach, I was greatly disconcerted by occasional interference with my observations. Although some animals displayed the rolling waves of the stomach wall with the utmost definiteness, others showed no movements whatever. The whole purpose of my effort, of course, was to see the waves and to learn their effects. Their failure to appear in animals which had been carefully prepared was a serious check on my progress. Only after some time did I note that the absence of activity was accompanied by signs of perturbation and that when serenity was restored the waves promptly reappeared. This observation, a gift for my troubles, led to a long series of studies on the effects of strong emotions on the body.—WALTER B. CANNON, M.D. *The Way of An Investigator.* New York, W. W. Norton & Co., Inc., 1945, p. 38.

Metabolism of Angiotensin II-I^{131} in Normotensive and Hypertensive Human Subjects

By Robert L. Wolf, M.D., Milton Mendlowitz, M.D., Stanley E. Gitlow, M.D., and Nosrat Naftchi, M.S.

BIOLOGICAL ASSAYS of angiotensin in the blood of patients with normal blood pressures, patients with benign essential hypertension, and patients with malignant hypertension indicate that there are significantly greater quantities of angiotensin in the subjects with benign essential hypertension than in the normotensive group and that the greatest quantities of angiotensin are present in the patients with malignant hypertension.[1-3] The present investigations were designed to determine the metabolism and rate of turnover of angiotensin in normotensive and hypertensive human subjects.

Methods

Angiotensin II (ileu-5-angiotensin II and val-5-angiotensin II)* was iodinated by the method of Pressman and Eisen[4] as modified by Newerly.[5] The angiotensin II-I^{131} was filtered through a Seitz filter and cultured before use. There was no apparent loss of hypertensive potency in the labeled angiotensin II preparations containing an average of 0.5 to 1.5 iodine atoms per molecule of angiotensin (1,036 molecular weight) as manifested by the hypertensive responses in the dog following intravenous administration of the labeled and unlabeled angiotensin II. Preparations containing less than 1.0 iodine atom per molecule of angiotensin II were used.

Doses of 50 to 150 μc. of angiotensin II-I^{131} were injected intravenously in human subjects. Urine was collected at 12-hour intervals thereafter. Heparinized blood samples were drawn from the patients at frequent intervals after administration of the angiotensin II-I^{131}. Radioactivity assays were performed on plasma, packed erythrocytes, urine, plasma precipitates, washed with 10 per cent trichloracetic acid (TCA) and plasma precipitates washed with 23 per cent sodium sulfate and ether.[6] Blood and urine radioactivities were assayed in a 5 ml.-capacity, well-type, scintillation counter with a sensitivity of 0.92×10^6 counts per minute per μc. I^{131} above a background of approximately 175 counts per minute. Blood concentrations of radioactivity were plotted as the products of the fraction of the administered dose per liter of plasma and the body weight in kilograms.

Paper electrophoresis was performed in barbital buffer, ionic strength 0.1, pH 8.6. Ten to one hundred microliters of material were applied to the cathode ends of strips of Whatman no. 3 MM filter paper, 37 by 500 mm., stretched across the vertical supports of the buffer vessels. After electrophoresis at 200 to 250 volts for 12 to 24 hours, the strips were dried for 45 to 50 minutes in an oven at 110 to 120 C. The strips were assayed for radioactivity in an automatic strip scanner with use of a thin window gas-flow counter with a sensitivity of 0.6×10^6 counts per minute per μc. I^{131} over a background of 40 counts per minute. Naphthalene black stain and 10 per cent acetic acid in methyl alcohol were employed to color the proteins in the strips.

Results

The concentration of radioactivity fell rapidly in the plasma and erythrocytes and rose in the urine following the intravenous injection of angiotensin II-I^{131}. The curve of erythrocyte radioactivity closely paralleled the curve of total plasma radioactivity. Approximately one third of the total blood radioactivity was in the erythrocytes and the remaining two thirds was in the plasma. When angiotensin II-I^{131} was added to plasma

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*Several preparations of angiotensin II-I^{131} labeled by Abbott Laboratories were employed in some experiments.

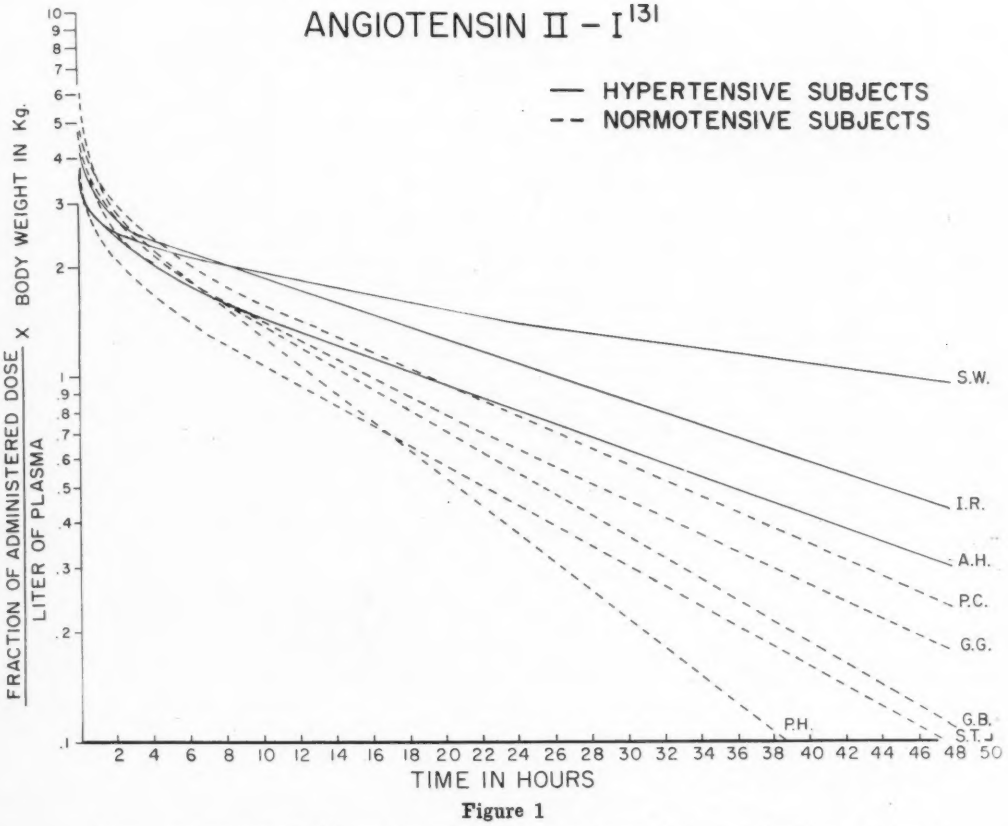

Figure 1

Plasma angiotensin II-I^{131} radioactivity (plasma radioactivity) as a function of time following intravenous administration.

in vitro, approximately 10 to 15 per cent was TCA precipitable. Plasma radioactivity samples taken up to 7 hours after injection were also TCA precipitable in the same order of magnitude (10 to 15 per cent). Several of the 24-hour samples of plasma had up to 20 per cent of the radioactivity in the TCA precipitate. Only 1 or 2 per cent of the urinary radioactivity was TCA precipitable. The urinary radioactivity migrated with the same mobility as iodine-131 and probably represented the radioactive end product of the metabolism of angiotensin II-I^{131}.

Not more than 3 per cent of the radioactivity was present in the globulin precipitate when angiotensin II-I^{131} was added to plasma and treated with 23 per cent sodium sulfate and ether. Plasma samples taken after the injection of angiotensin II-I^{131} and treated in a similar fashion also revealed similar small quantities of radioactivity in the globulin precipitates.

Figure 1 summarizes the plasma radioactivity at various intervals of time following the intravenous administration of angiotensin II-I^{131} in all subjects. The curves illustrate the relatively high radioactivity remaining in the plasma of hypertensive subjects. This group was composed of two patients with essential hypertension and one patient (S.W.) with malignant hypertension with grade-IV retinopathy. A more rapid disappearance of plasma radioactivity was observed in the five normotensive control patients. The rate of

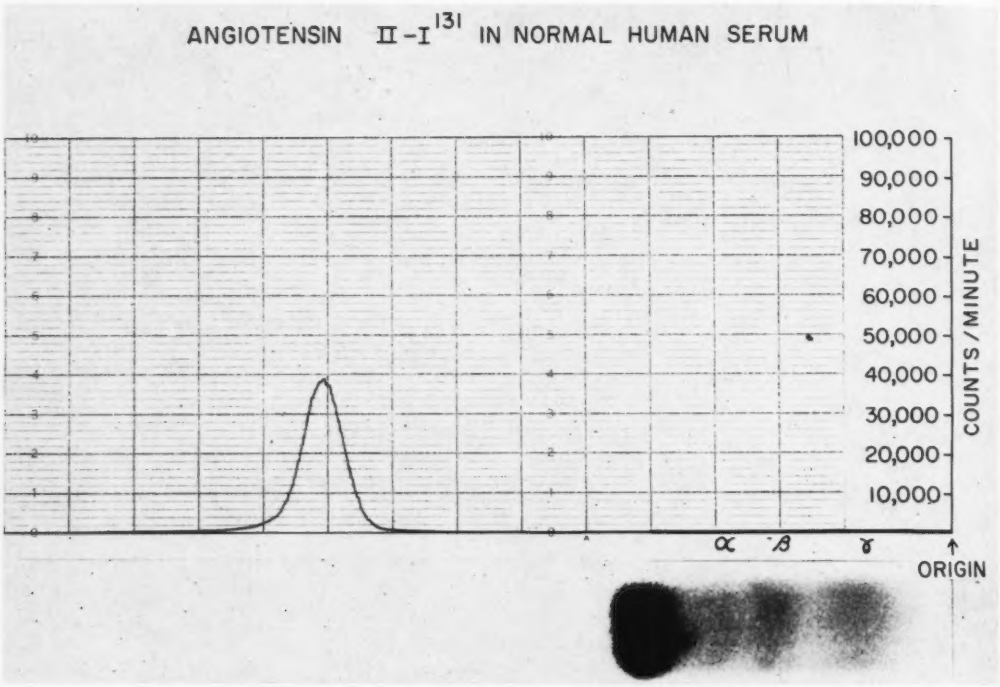

Figure 2

Paper radioelectrophoretogram of angiotensin II-I^{131} in control human plasma. The angiotensin II-I^{131} migrated approximately 7 cm. further than the albumin.

disappearance of plasma radioactivity appeared to be correlated, therefore, with the presence or absence of hypertensive disease.

When small quantities of angiotensin II-I^{131}, either alone or mixed with 20 to 50 μl. of normal human plasma or serum in vitro were analyzed by paper electrophoresis, the radioactivity migrated approximately 5 to 7 cm. further than the albumin (fig. 2). The distribution of radioactivity formed a smooth, symmetrical peak without skewing or distortion. Similar results were obtained on radiochromatography effected by opening the top of the electrophoretic apparatus and running the voltage supply at 600 volts. The electrophoretic and chromatographic behavior of the plasma radioactivity following the intravenous administration of angiotensin II-I^{131} was identical with that described in the in vitro control experiments, and this material represented, therefore, angiotensin II. There was also no difference in the electrophoretic mobility of tracer amounts of angiotensin II-I^{131} alone or in a mixture of 50 μl. of urine before and after incubation at 37 C. for 24 and 48 hours.

Table 1 summarizes the "apparent spaces of distribution" 30 to 45 minutes after angiotensin II-I^{131} injection and the half time of degradation of plasma radioactivity. Characteristic differences were observed between the hypertensive and the control groups. The five normotensive subjects had smaller apparent spaces of distribution and more rapid degradation rates of angiotensin II than the two subjects with benign essential hypertension or the one subject with malignant hypertension.

Discussion

The manipulations involved in the labeling of angiotensin II did not alter the electrophoretic, chromatographic, or biologic proper-

ties of the peptide. The time curves of plasma radioactivity were, therefore, a manifestation of the distribution and metabolism of the angiotensin II-I^{131}. These data may be utilized to approximate various parameters of angiotensin II-I^{131} metabolism. The average whole blood concentrations of angiotensin II have been roughly assayed by Kahn and his associates with an average recovery of 50 per cent.[3] These results indicated a rough plasma angiotensin II concentration of 0.018 μg. per liter in normotensive subjects, 0.038 μg. per liter in subjects with benign essential hypertension, and 0.32 μg. per liter in malignant hypertension subjects. The mean values for the apparent volumes of distribution of angiotensin II were approximately 23 liters in the normotensive subject and 29 liters in subjects with benign and malignant hypertension. The total amounts of angiotensin II that were present in the body and that were readily exchangeable with the blood angiotensin II averaged approximately 0.41 μg. in the normotensive subject, 1.10 μg. in the two subjects with benign essential hypertension, and 9.3 μg. in one malignant hypertensive subject. Although these values may appear low, it should be remembered that intravenously administered injections of angiotensin II in a dosage of 1 to 2 μg. produced a detectable blood pressure elevation.[7]

The rate of degradation of angiotensin II lies between the rapid rates of hydrocortisone, adrenocorticotropic hormone, and insulin (with half times of approximately 30 minutes) and thyroxin, which has a half time of approximately 7 days.[8–11] A relatively slow degradation rate of angiotensin II insures a steady angiotensin II blood concentration.

The slower rate of degradation of angiotensin II-I^{131} from the circulation of hypertensive subjects than from that of normotensives indicates that the degradation rate is a limiting factor governing the concentration of angiotensin II in the body fluids. Since the endogenous blood concentration of angiotensin II remained essentially unchanged throughout the course of the experiments, steady-state conditions may be assumed, and therefore the rate of synthesis was equal to the rate of degradation of angiotensin II. The present study indicated that the high concentrations of angiotensin II in the blood and the large total exchangeable pools of angiotensin II in hypertensive subjects were related to a slow rate of degradation.

Table 1

Space of Distribution and Degradation Rate of Plasma Radioactivity after Angiotensin II-I^{131} Administration

Subject	Diagnosis	Space of distribution per cent body weight	Rate of degradation T ½ (hr.)	Rate of degradation % hr.
G. B.	Control	36	10	6.93
S. T.	Control	42	11	6.30
P. H.	Control	31	8	8.66
G. G.	Control	28	12	5.77
P. C.	Control	24	12	5.77
Mean		32.2	10.6	6.69
A. H.	Essential hypertension	45	14	4.95
I. R.	Essential hypertension	36	17	4.07
Mean		41	15.5	4.51
S. W.	Malignant hypertension	42	37	1.87

Summary and Conclusion

Many patients with hypertension have greater concentrations of the peptide, angiotensin II, in their blood than normotensive persons.

Angiotensin II-I^{131} has been intravenously administered to normotensive and hypertensive human subjects.

The plasma radioactivity after injection has been studied by electrophoretic and chemical analysis and indicates that the rate of degradation of angiotensin II-I^{131} is slower in hypertensive than in normotensive subjects.

Acknowledgment

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Sir Thomas Browne
1605–1682

Critics from Johnson to Walter Pater have put on record their estimate of Browne and of his place in literature. Among these for keenness of appreciation Pater takes the first rank. Lamb and Coleridge dearly loved the old Norwich physician, in whom they found a kindred spirit. In America the New England writers, Ticknor, Fields, Holmes, and Lowell, were ardent students of his works. Lowell in particular is fond of apt quotations from him, and in one place speaks of him as "our most imaginative mind since Shakespeare" . . . The growing popularity of Browne's writings testifies to the assured position he holds, if not in the hearts of the many, at least in the hearts of that saving remnant which in each generation hands on the best traditions of our literature. We, who are members of his profession, may take a special pride in him. Among physicians, or teachers of physic, there is, perhaps, but one name in the very first rank. Rabelais stands apart with the kings and queens of literature. Among the princes of the blood there are differences of opinion as to rank, but Sir Thomas Browne, Holmes, and John Brown of Edinburgh form a group together high in the circle. Of the three, two were general practitioners; Oliver Wendell Holmes only in the early part of his life, and for forty years a teacher of anatomy; but all three have far closer ties with us than Goldsmith, Smollett, or Keats, whose medical affiliations were titular rather than practical.—SIR WILLIAM OSLER. *A Way of Life and Other Selected Writings.* New York, Dover Publications, Inc., 1951, p. 57.

Vascular Malformation Overlying the Pulmonary Artery Simulating a Patent Ductus Arteriosus

By CALVIN B. ERNST, M.D., KARL P. KLASSEN, M.D., AND JOSEPH M. RYAN, M.D.

THE PRESENCE of an asymptomatic patent ductus arteriosus is usually suspected on the basis of auscultatory findings, and the diagnosis is supported by electrocardiography and roentgenography. Other vascular and cardiac lesions that produce continuous murmurs to the left of the upper sternum are usually symptomatic and are associated with additional changes requiring cardiac catheterization and contrast studies for a final diagnosis. Aneurysmal dilatation of the coronary vessels associated with arteriovenous fistulas give rise to murmurs simulating patent ductus arteriosus. These anomalies may be entirely asymptomatic or cause the symptoms of myocardial ischemia. The following is a case report of a coronary-pulmonary artery fistula not involving the myocardium and simulating a patent ductus arteriosus.

Case Report

S. S., hospital no. 691383. An 18-year-old college girl was referred for evaluation of a heart murmur first heard 6 months previously during a routine examination. Growth and development since birth had been normal and the patient had been asymptomatic.

On physical examination the abnormal physical findings were limited to the heart. The temperature was normal with a pulse of 80 and a respiratory rate of 20 per minute. The blood pressure in the right arm was 110/70 mm. of mercury, and in the left arm 150/72 mm. The heart was not enlarged. The point of maximum cardiac impulse was in the fifth intercostal space 1 cm. medial to the left midclavicular line, and a thrill was not felt. A continuous grade III systolic, early grade II diastolic, crescendo-decrescendo murmur was heard loudest in the second intercostal space 2 cm. to the left of the sternum. The murmur was well localized and was not transmitted to the axilla, back, or precordium; it was rather soft and could be heard best with the patient leaning forward. There was no clubbing or cyanosis.

Laboratory determinations were all within normal limits. Cardiac fluoroscopy showed the heart to be normal in size and general configuration. The electrocardiogram showed only slight right axis deviation.

The consensus was that this represented a small patent ductus arteriosus. It was thought that thoracotomy was indicated because of the location and type of the murmur. Through a left posterolateral thoracotomy, the mediastinum was exposed in the region of the ductus arteriosus, and the thrill was located more centrally along the pulmonary artery. Pressure on the mediastinum in the region of the ductus did not obliterate the thrill, whereas pressure on the proximal pulmonary artery did. The mediastinum was opened and a fibrous ligamentum arteriosum was found; it was transected and found not to be patent.

When the pericardium was opened posterior to the phrenic nerve, multiple serpiginous dilated vessels were seen over the base of the pulmonary artery extending to the point where the pulmonary artery leaves the pericardium (fig. 1). Aneurysmal dilatation was present in several areas on the pulmonary artery where a thrill was felt. The vascular anomaly did not involve the myocardium. With gentle compression of the aneurysm, the thrill disappeared. The tortuous vessels were fed by three arterial branches, two of these coming from the right and left coronary arteries, and one from the region of the pericardiophrenic artery as the pulmonary artery leaves the pericardium. There were other small branches from accessory vessels from the left atrium and the conus artery. Temporary occlusion of the feeder vessels produced no observable color changes in the myocardium and no abnormalities in the electrocardiographic tracing of the monitor.

A small incision was made in one of the aneurysmal dilatations, and bright red blood spurted at systolic pressure. The feeders were then ligated with collapse of the aneurysms and disappearance of the thrill. The patient did well postoperatively and was discharged seven days later without the heart murmur.

Discussion

Excellent discussions concerning the rela-

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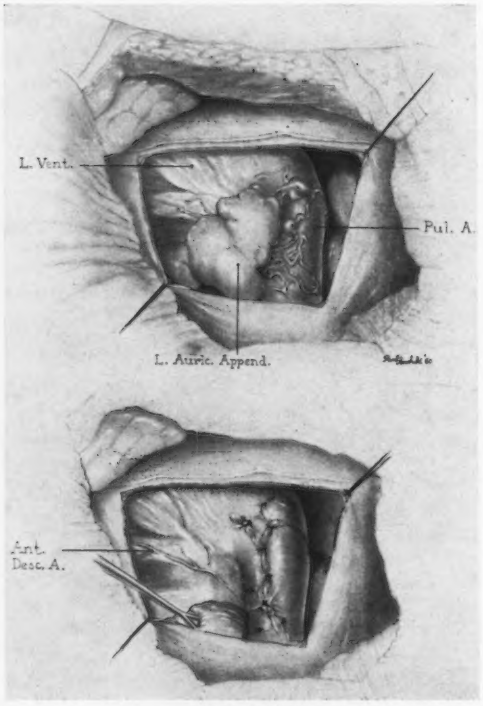

Figure 1

Appearance of coronary-pulmonary artery fistula prior to and subsequent to multiple ligation.

tively rare congenital coronary arteriovenous fistulas have appeared in the literature.[1-5] The majority of the reported cases represent arteriovenous fistulas with flow from the involved coronary arteries to the right atrium, right ventricle, or pulmonary artery, thus representing a left-to-right shunt. The diagnosis was based on autopsy findings prior to 1947, when Biörck[6] reported the first such case diagnosed and treated by ligation during a thoracotomy performed for a suspected patent ductus arteriosus. Since that time the diagnosis of coronary arteriovenous fistula has been made at the time of thoracotomy.[5, 7] Several cases have been reported in which a correct diagnosis was made on the basis of cardiac catheterization[5] and angiocardiography.[3, 5]

The present case differs from previously reported ones in that the arteriovenous malformation did not involve the walls of the ventricle or atrium but only the main pulmonary artery. Blood flow was in the direction of the pulmonary artery, as proved by the presence of high pressure oxygenated blood in the supplying branches. Both coronary vessels, which were normal in distribution and size, supplied branches to the fistula and there was an additional vessel coming from the pericardiophrenic artery or possibly from branches of the bronchial artery along the pulmonary artery.

It has been established that the walls of the pulmonary artery and veins within the pericardium derive their blood supply from branches of the coronary vessels[8] while the extrapericardial portion of the pulmonary artery and veins receive their blood supply from the bronchial arteries.[9] These arterial and venous vasa vasorum do not communicate with the lumen of the pulmonary artery under normal conditions as do vasa vasorum of the systemic arteries.[9] In pulmonic stenosis in tetralogy of Fallot or following thrombosis of the pulmonary vessels, perforation of the wall of the pulmonary vessels by these vasa vasorum can and probably does occur. In the present case, however, we were unable to determine the reason for such fistula formation; there was no evidence of pulmonary stenosis or of previous thrombosis. The small size of the aneurysm and the supplying vessels explained the absence of symptoms and the normal cardiac size and pulmonary vascularity. Catheterization of this patient might have indicated the presence of this small shunt; retrograde aortography of good quality, however, would have led to a correct preoperative diagnosis.

Summary

An arteriovenous fistula with aneurysmal dilatation involving branches of both coronary vessels and the pulmonary artery is discussed.

The malformation was limited to the main pulmonary artery and presented a small left-to-right shunt without symptoms.

Ligation of the supplying vessels resulted in the disappearance of a murmur typical of a patent ductus arteriosus.

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Constancy of the External Environment

The regulatory devices of our modern laboratories have not yet succeeded in rivaling the ocean. Singly, certain conditions, for example, temperature, alkalinity, and concentration, may be more accurately regulated by man, though on a small scale only; but the regulation of all such properties together is not yet possible. The only known improvement upon the ocean is the body of a higher warm-blooded animal. Here, however, the processes of organic evolution have begun with the ocean, and in several respects merely perfected existing arrangements.—Lawrence J. Henderson. *The Fitness of the Environment.* New York, The MacMillan Co., 1924, p. 186.

Obliterating Left Ventricular Mural Thrombosis

By JACOB ZATUCHNI, M.D., AND KEE TON TAN, M.D.

HEREIN is reported a case in which a left ventricular mural thrombus was so large as almost completely to obliterate the left ventricle. Such an occurrence, to our knowledge, has never been reported.

Case Report

A 64-year-old white man, blind since birth, considered himself well until March 1960. Because of progressive weakness, shortness of breath upon effort, and swelling of the ankles, he entered Episcopal Hospital on June 13, 1960. Cardiac therapy was intensified and left thoracentesis was done on several occasions. The fluid was serosanguineous in character. Pleural biopsy, with a Vim-Silverman needle, disclosed only fibrous tissue. He was discharged on July 18, 1960.

Shortly thereafter, shortness of breath again increased, and ankle edema and left pleural effusion reappeared. He was re-admitted to Episcopal Hospital on August 17, 1960. Findings were similar to those previously observed.

The blood pressure was 100/80 mm. Hg. The temperature was normal. There was bilateral optic atrophy. The jugular veins were slightly distended. The cardiac impulse was not palpable. Heart sounds were distant and normal in quality, rate, and rhythm. There were no murmurs. Signs of left pleural effusion were present. The abdomen was negative; the liver and spleen were not felt. There was moderate pitting edema of the legs and feet.

The hemoglobin and electrolytes were normal, the serologic tests for syphilis were negative, and the serum glutamic oxaloacetic transaminase was normal.

Roentgenogram of the chest (fig. 1) revealed increased size of the cardiac silhouette, involving mainly the left ventricular salient. The upper border of the left ventricle tended to be concave and bulged laterally into the density produced by a left pleural effusion. On fluoroscopy, following removal of most of the pleural fluid, no pulsation could be seen over the left ventricle. There were faint pulsations of the other borders of the cardiac silhouette. There was no change in the cardiac silhouette with either the Mueller or Valsalva maneuver. There was no intracardiac calcification. The pulmonary vascular markings were slightly increased. The findings were interpreted as consistent with pulmonary congestion, left pleural effusion, and enlargement of the heart predominantly of the left ventricle, which was probably aneurysmal and possibly associated with mural thrombosis. Additional pericardial disease could not be excluded.

The electrocardiograms (fig. 2) were interpreted, in the absence of change, as consistent with extensive anterior myocardial fibrosis, probable left ventricular aneurysm, left atrial enlargement, and digitalis effect.

Left thoracentesis on several occasions yielded serosanguineous and later dark amber fluid. The underlying lung appeared compressed but was otherwise not remarkable.

Dyspnea and edema of the lower extremities gradually lessened and the patient lost 13 pounds. On September 4, 1960, while resting in bed, he suddenly became tachypneic, pale, and cyanotic, and died.

Autopsy Findings

The right pleural cavity was obliterated by a chronic fibrous pleuritis. The left pleural cavity contained 600 ml. of fluid, dark amber in color. The visceral pleura overlying the left lower lobe was thickened, and the underlying lung was firm, contracted, and congested. Microscopically the lung showed marked vascular congestion with extravasation of erythrocytes into the alveoli, which were edematous and contained "heart failure" cells. The pulmonary vessels were patent. There was some thickening of the walls of the smaller branches of the pulmonary artery.

The heart weighed 610 Gm. The pericardium was thickened and fused anteriorly with the epicardium of the left ventricle. The left atrium was slightly enlarged. The entire anterior wall of the left ventricle was thin and fibrotic, and tended to bulge somewhat. The walls of the remaining portion of the left ventricle were reduced in thickness.

Arising from the anterior wall of the left ventricle and extending into and almost obliterating the left ventricle was a large, firm, fibrotic, and layered thrombus. The diameter of the thrombus was 10 cm. The capacity of the remaining left ventricular cavity was estimated to be approximately 30 ml. Microscopically there was extensive myocardial fibrosis but no evidence of acute myocardial infarction. The thrombus itself was fibrotic, and its union with the myocardium was indistinguishable.

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No other thrombi were found. The cardiac valves were normal. The coronary arteries exhibited a moderate degree of generalized narrowing and sclerosis, and the anterior branch of the left coronary artery was completely occluded by an organized atheroma, 5 ml. in length, beginning 2.5 cm. from the ostium. The entire aorta showed mild atherosclerotic changes.

The liver weighed 1,100 Gm. It was nutmeg in appearance and revealed dilatation and congestion of the central veins and adjacent sinusoids. The surrounding hepatic cells showed degenerative change. The spleen was firm and weighed 120 Gm. There was marked congestion and a slight increase in fibrous tissue.

Sections of the heart, liver, and spleen are shown in figure 3.

Discussion

It was apparent from the chest roentgenogram that there was an aneurysm of the left ventricle.[1] The basis for the aneurysm was considered clinically to be myocardial fibrosis secondary to occlusive coronary artery disease, the absence of pain notwithstanding. Indeed, many cases of cardiac aneurysm have been reported to sustain a silent myocardial infarction and to present with congestive heart failure of insidious onset.[2] Interestingly, however, although the patient steadfastly denied having any pain, his family, following his death, related, in response to direct questioning, that he had had bouts of substernal pain for several months prior to his demise. Curiously, it was his wish that no physician should be informed of this distress because he feared hospitalization.

The aneurysm displayed no motion. A cardiac impulse was not palpable, and the left ventricular portion of the cardiac silhouette was seen by fluoroscopy not to pulsate. The absence of pulsation was thought to be due to intrinsic myocardial disease and possibly to mural thrombosis and even pericardial restriction, which frequently occur in left ventricular aneurysms arising from occlusive coronary artery disease.[3, 4] Unfortunately, his condition did not permit study of the heart by contrast roentgenography, by which diagnostic conclusions might have been possible.[5-7]

At autopsy, the entire anterior wall of the left ventricle was reduced to a fibrous shell. Arising from it and almost filling the left ventricle was a huge, organized, and layered thrombus.

Figure 1

Posteroanterior chest roentgenogram. The cardiac silhouette is increased in size and its shape suggests mainly left ventricular enlargement. The upper border of the left ventricular portion of the cardiac silhouette is concave and sweeps outward, due to aneurysmal formation, into the density produced by a left pleural effusion.

We have been unable to find in the literature a similar occurrence, although in the case reported recently by Dexter, Lawton, and Raynolds,[8] the left ventricular mural thrombus may possibly have been as large. Their case had an aneurysm, 18 cm. in diameter, described as being completely filled with a mural thrombus. Another might be the case reported by Shennan and Niven.[9] In both of these cases, although it is not clear if the thrombus was restricted to the aneurysm or filled the ventricular cavity, illustrations show, indeed, a huge thrombus.

Such an obliterating thrombus of the left ventricle would be anticipated to produce severe restriction of inflow similar to that

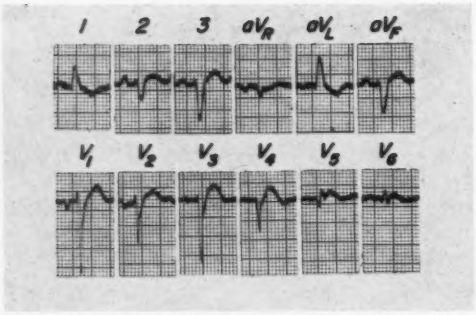

Figure 2

Electrocardiogram showing sinus rhythm and findings consistent with left atrial enlargement, extensive anterior myocardial fibrosis, probable aneurysm, and digitalis effect.

occurring in mitral stenosis. Indeed, the electrocardiogram showed signs consistent with left atrial enlargement, which was found at necropsy, and the pulmonary arterioles showed changes consistent with pulmonary hypertension.

Forward flow from the left ventricle would also be expected to be seriously compromised. The fatigue, pallor, and low blood pressure bespoke a low cardiac output.

Similar findings occur, of course, in many other conditions,[10] including left ventricular aneurysm alone.[11] In the presence of left ventricular aneurysm, a clue to the existence of mural thrombosis is thromboembolism, which occurs in almost two thirds of the cases.[3] It is not always present, however, and it may also occur in the absence of clinical manifestations and in the absence of mural thrombosis.[3]

Another clue to the presence of associated mural thrombosis is absence of pulsations of the left ventricular aneurysm.[1] Pulsations of a left ventricular aneurysm are characteristically paradoxical.[12, 13] The involved wall of the left ventricle is fibrous and bulges with each ventricular systole. The presence of a mural thrombus would be anticipated to dampen such an outward thrust. The reliability of this sign in diagnosing associated mural thrombosis is questionable, however, for other conditions, like dilatation or

Figure 3

Gross sections of the liver (upper left), *spleen* (upper right), *and heart viewed from above. There was chronic passive congestion of the liver and spleen, which were firm. In the section of heart, note the thin fibrous residue of the anterior wall and the huge, fibrous, layered thrombus arising from it and almost obliterating the left ventricle. The remaining cavity has been increased by distortion for photographic purposes. The subjacent muscle is the septal portion of the left ventricle.*

pericardial effusion, may produce similar dampening. Also, to our knowledge, there has been no systematic study made of the pulsations of left ventricular aneurysm alone compared with those associated with mural thrombosis. Certain it is that pulsations do not exclude mural thrombosis.[14] Other roentgenographic signs suggestive of left ventricular mural thrombosis include increased density and even calcification,[15] but these are very rare.

For these reasons, clinical recognition is difficult. Nevertheless, knowledge of its occurrence can lead to a strong clinical suspicion of its presence which perhaps may be established with certainty by contrast roentgenography.

Summary and Conclusions

A case is recorded of a huge mural thrombus that encroached upon and almost obliterated the left ventricle. There was underlying occlusive coronary artery disease with extensive myocardial fibrosis and aneurysm formation. Clinical manifestations, other than

those produced by a persistent left pleural effusion, were similar in effect to any condition producing severe restriction of left ventricular inflow and outflow. A clue to its presence was absence of left ventricular pulsations.

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The very ingenious *Dr. Hales* writes me, that, having many years since, tied a ligature about a frog's neck, to prevent any effusion of blood, he cut off its head, and, thirty hours after, observed the blood circulating freely in the web of the foot: the frog also at this time moved its body when stimulated: but, on thrusting a needle down through the spinal marrow, the animal was strongly convulsed, and, immediately after, became motionless.—Robert Whytt. *Physiological Essays.* Edinburgh, 1755, p. 176.

CLINICAL PROGRESS

The Carotid Sinus

Clinical Value of Its Stimulation

By BERNARD LOWN, M.D., AND SAMUEL A. LEVINE, M.D.

STRETCH OR BARORECEPTORS on the arterial and venous side of the circulation play an integral role in regulating certain key cardiovascular functions. The only receptors that can readily be affected from the outside are the carotid sinuses, situated at the bifurcation of the common carotid arteries. Massage or pressure over these areas may change significantly heart rate, heart rhythm, and systemic blood pressure.

Manipulation of the carotid sinus can be accomplished at the bedside. When done properly the maneuver carries little risk. It frequently serves as an important diagnostic aid and may be a definitive therapeutic measure. At times it constitutes the only means of correctly diagnosing the underlying cardiac disturbance. In recent years insufficient attention has been given to the carotid sinus test. The object of the present report is to summarize current physiologic knowledge of the carotid sinus, to indicate the effects of stimulation of this area in normal man, to emphasize its prompt therapeutic value in some cardiovascular conditions, to delineate the valuable clinical information, which such stimulation may provide, and to point out certain hitherto unreported insights that this test affords.

Historical Considerations

The Greeks may have been aware that compression of the carotid artery affected cerebral function, for the term carotid derives from *karos,* a Greek word meaning heavy sleep. The earliest medical report is that of Parry in 1799,[1] who noted that pressure on the bifurcation of the common carotid artery produced dizziness and slowing of the heart. A similar observation was made by Czermack in 1866.[2] He found that pressure upon the carotid swelling at the level of the upper margin of the sternocleidomastoid muscle induced temporary bradycardia. He ascribed this to mechanical stimulation of the adjoining vagus trunk by the carotid bulb. In 1870 Concato[3] pointed out that bradycardia occurred only if the bifurcation of the common carotid was compressed while pressure on the cervical vagus alone was without such effect. This finding was ignored, and Czermak's view prevailed for many years and was known as the "vagus pressure test" (Vagusdruckversuch) of Czermak.

Animal experiments in the nineteenth century demonstrated that lowering arterial pressure in the head and neck produced tachycardia, whereas elevation of pressure in these vessels was followed by bradycardia and a fall in systemic pressure.[4] This led to the conclusion that cardiac and vasomotor centers in the medulla were directly sensitive to pressure changes in the nutrient arteries. Siciliano[5] and Pagano[6] however demonstrated that ligation of all branches of the internal and external carotid arteries supplying the medullary centers did not change heart rate or vasomotor tone. Sollman and Brown[7] further demonstrated that traction of the carotid arteries in the absence of stimulation of the vagus nerve reduced arterial pressure and

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slowed the heart rate. Notwithstanding the definite nature of these findings, the hypothesis that a cardioregulatory and vasomotor center in the medulla was directly sensitive to pressure was entertained until recently.[8]

The painstaking work of Hering[9, 10] in the early 1920's brought general recognition of the reflex nature of carotid sinus stimulation. When the vagus nerve was separated from the adjoining vessels, mechanical pressure upon the bifurcation of the common carotid artery continued to produce the same degree of bradycardia. He and his co-workers[11, 12] further demonstrated that the bifurcation of the common carotid is richly supplied with sensory nerves. These nerves emerge from the adventitia as spiral fibers to form the sinus nerve of Hering, which joins the glossopharyngeal nerve. Thus, a direct afferent nerve connection was shown to exist between the carotid sinus and the medullary centers. When the sinus nerve was divided or cocainized, raising or lowering pressure in the common carotids resulted in no reflex changes in the heart. The conclusions of Hering were confirmed by the detailed anatomic studies of De Castro,[13] who showed profuse arborization of sensory receptors lying among the collagen fibers of the adventitia of the carotid sinus. The physiologic significance of the carotid sinus as a part of the baroreceptor system of the body was documented by the meticulous experimentations of Heymans and Neil.[14] Wassermann was the first to observe that stimulation of the carotid sinus was effective in terminating some episodes of acute pulmonary edema[15] and relieving angina pectoris.[16] Clinical attention to the carotid sinus as an area responsible for syncopal attacks was high-lighted by the work of Weiss and Baker.[17]

Physiology of the Carotid Sinus Pressoreceptors

The most extensively studied and best known set of pressor reflexes in the circulation are those originating from the carotid sinuses. These pressoreceptors are anatomically and functionally distinct from the chemoreceptors situated in the adjoining carotid bodies.[18] While the carotid artery possesses other baroreceptors, those in the carotid sinus play a key role. The afferent impulses generated in the sinus reach the glossopharyngeal nerve by the nerve of Hering. This nerve carries impulses not only from pressoreceptors located in the carotid sinus and in the region of the carotid bifurcation, but also from the chemoreceptors of the carotid body. Cutting the nerve of Hering thus inactivates both the carotid sinus and the carotid body.

Bradycardia, hypotension, and apnea result when electrical stimulation is limited to the pressoreceptor fibers of the nerve of Hering. These baroreceptors are activated by stretching or deformation of the wall of the carotid sinus in which the nerve endings are embedded. Hauss and co-workers[19] showed convincingly that when deformation of the sinus wall was prevented, a rise in endosinus pressure was without effect.

Under physiologic conditions, stretching of the sinus is initiated by a rise in carotid artery blood pressure, whether the rise in pressure is static[12] or is generated by pulsatile flow.[20] Pulsatile stimuli are far more effective than sustained pressure in arousing baroreceptor activity.[21, 22] The carotid sinus reflex is initiated at a pressure of 60 mm. Hg. With each systole there is a burst of activity in the sinus nerve. As carotid pressure rises, the frequency and duration of firing are increased with progressive recruitment of discharging units.[23, 24]

Changes in the carotid sinus wall itself may affect the sensitivity of the baroreceptor. Application of epinephrine to the wall of the carotid sinus caused reflex hypotension.[25] A large variety of drugs that induce smooth muscle contraction have a similar effect.[14] When all arterial branches to the carotid sinus were ligated and the common carotid arteries were opened just proximal to the bifurcation, topical application of norepinephrine induced reflex hypotension, which was abolished by section of the sinus nerve.[26] These effects can be blocked by adrenolytic agents.[14] Actual contraction of the sinus wall has been observed upon addition of epineph-

rine to Tyrode's solution bathing the excised suspended structure.[27] When, however, the carotid sinus is perfused with blood containing increased concentration of epinephrine, baroreceptor sensitivity is not enhanced.[14] These observations suggest that responsiveness of the baroreceptor mechanism depends upon the state of tension in the wall itself.

Stimulation of the carotid sinus also induces changes in the sympathetic nervous system. When endovascular pressure in the sinus is increased, the persistent tonic discharge traversing sympathetic nerves from the stellate ganglion to the heart is diminished.[28] If the increased pressure within the sinus is maintained, complete inhibition continues for some seconds, after which there is escape and return of sympathetic discharge. The duration of inhibition and the speed of escape are a function of the pressure level. Reflex inhibition is bilateral. When one side is stimulated, discharge decreases from both stellate ganglia. When the carotid sinus is suddenly distended, vagal activity accounts for the initial slowing; however, decreased sympathetic activity, which emerges more gradually, becomes the major restraining influence with continued stimulation.[29]

The effector reflex pathway resulting from an increase in endosinus pressure has been extensively studied.[14] The bradycardia is due to activation of cardio-inhibitory innervation and inactivation of the cardio-accelerators. The hypotension results from decreased activity of the vasoconstrictor sympathetic center. There are also respiratory inhibition, bronchoconstriction, and pulmonary hypotension.[18] The picture, therefore, is that of massive inhibition of medullary centers. An exception is the increased performance of cardio-inhibitory nerves. This may be due to release of their inhibition by the depression of the cardio-accelerators. In addition to hypotension, the circulatory consequences consist of pooling of blood in the periphery due to venous dilatation and reduction in the cardiac output.[18]

When the carotid sinus is inactivated by sectioning the nerve of Hering, changes opposite to those described above follow. Tachycardia, hypertension, and some hyperpnea develop. The hypertension is due both to increased vascular resistance brought about by augmented activity of the vasomotor center and to an increase in the cardiac output.[30-33] An increased discharge in all sympathetic nerves to the heart and an enhanced liberation of catecholamines by the adrenal glands also occur.[14]

Current concepts of the physiologic significance of the carotid sinus pressoreceptors remain essentially those outlined by Hering, the discoverer of the reflex. The two carotid sinuses, together with the receptors in the aortic arch, form a unified depressor system. These baroreceptors are stimulated by the systolic surges of intravascular pressure to emit inhibitory impulses that continuously restrain the cardio-accelerator and vasoconstrictor centers within the medulla. When intravascular pressure rises, these receptors become more active. Conversely, with reduction of systemic blood pressure, the centers become inactive. The reflex originating from these pressoreceptors is depressed or paralyzed by hypocalcemia, anoxemia, high spinal anesthesia, narcotics, and pulmonary hyperventilation.[18]

Reduced activity of the carotid and aortic baroreceptors that occurs with a fall in systemic pressure also plays a vital role in homeostasis. Venoconstriction is probably the most important consequence of such inactivity. Since the veins contain about 60 per cent of the blood volume, a reduction of the venous capacity by only 1 or 2 per cent will increase diastolic inflow to the heart. The decrease in venous capacity is associated with reflex tachycardia. This combination of adjustments is effective in sustaining the cardiac output. The simultaneous increase in peripheral arteriolar resistance in the skin and splanchnic areas that accompanies diminished baroreceptor activity aids in distributing blood to cerebral and coronary circulations, which are themselves independent of the reflex vasoconstriction.

Carotid Sinus Stimulation in Normal Man

In the normal person, carotid sinus stimulation results in respiratory and cardiovascular changes. Hyperpnea usually follows digital pressure to the carotid sinus area with an increase in depth but not in rate of respiration.[34] This response is independent of the subject's age or sex and appears unrelated to simultaneously induced cardiovascular changes. Once pressure is applied, the depth of the respiratory excursion begins to increase within 5 to 20 seconds and continues until a peak is reached within 45 to 90 seconds. Prolonged stimulation may result in a phasic type of breathing simulating Cheyne-Stokes respiration. Painful stimuli in the neck region or compression of the carotid artery below or above the carotid sinus area do not evoke this change in ventilation. The respiratory reflex persists during barbiturate anesthesia.

Galdston and co-workers[34] have shown that procainization of the carotid sinus area that prevents the respiratory reflex also abolishes hyperventilation from injection of sodium cyanide. The cyanide ion in low concentration stimulates respiration through action on chemoreceptors of the carotid and aortic bodies. These workers have suggested that the respiratory reflex is due to interference with blood supply to the carotid body which lies adjacent to the carotid sinus. In support of a different mechanism for the respiratory and cardiovascular reflexes is the observation that when the carotid sinus is stimulated, as a local anesthetic effect wears off, the respiratory response returns before the cardiac response. Furthermore, in animal experiments apnea rather than hyperpnea occurs when stimulation is limited to the baroreceptor fibers of the carotid sinus.[18]

The cardiovascular effects are upon the sinoatrial pacemaker, the atrioventricular (A-V) conduction system, and the blood pressure. Cohn and Lewis[35] first reported upon the electrocardiographic effects of vagal stimulation. The changes, in order of their frequency, are the following: sinoatrial slowing, atrial conduction defects with changes in amplitude, duration and morphology of the P wave, sinoatrial bradycardia with rates ranging from 30 to 50 per minute, prolongation of P-R interval, A-V block, sinoatrial arrest, nodal escape, complete asystole, and ventricular ectopic beats. No changes have been observed in the QRS complex. The effects upon the sinoatrial pacemaker and the conduction system are mutually independent.

In a study of the effect of carotid sinus stimulation in 67 subjects without heart disease, Purks[36] noted slowing of the sinus rate in 75 per cent, A-V conduction defects in 10 per cent, ventricular standstill in 4 per cent, and atrial standstill in 3 per cent. A response was elicited in 82 per cent of those over 40 years of age, but in only 18 per cent under 40. In a recent study of 40 normal men,[37] the carotid sinus was compressed for 30 seconds. The age range of this group was 25 to 58, with a mean age of 38. Interatrial block occurred in 30 instances, sinoatrial bradycardia in 14, and P-R prolongation in 12. Ventricular asystole, varying from 2.0 to 5.7 seconds in duration, was produced in nine subjects. Pressure on either side was equally productive of electrocardiographic alterations. Subjective manifestations including syncope, nausea, and light headedness were found in 25 per cent.

When constant pressure is exerted on the carotid sinuses, maximum prolongation of the P-P interval is often observed promptly with the first cardiac cycle after the onset of stimulation.[38] When such pressure is applied for 30 seconds or more, the sinoatrial rate often returns to its control level within 10 to 15 seconds. With release of pressure the heart rate may accelerate slightly. This is probably due to sympathetic rebound, since there is a reduction in impulse conduction in the sympathetic chain during carotid sinus stimulation.[28]

A depressor vasomotor reflex occurs in man upon stimulation of carotid sinus.[17, 39, 40] Mandelstamm and Lifschitz[41] induced a fall in systolic pressure of at least 10 mm. Hg in 60 per cent of 335 subjects. This was particularly marked in patients having either arteriosclerosis or hypertension. In 103 aged and

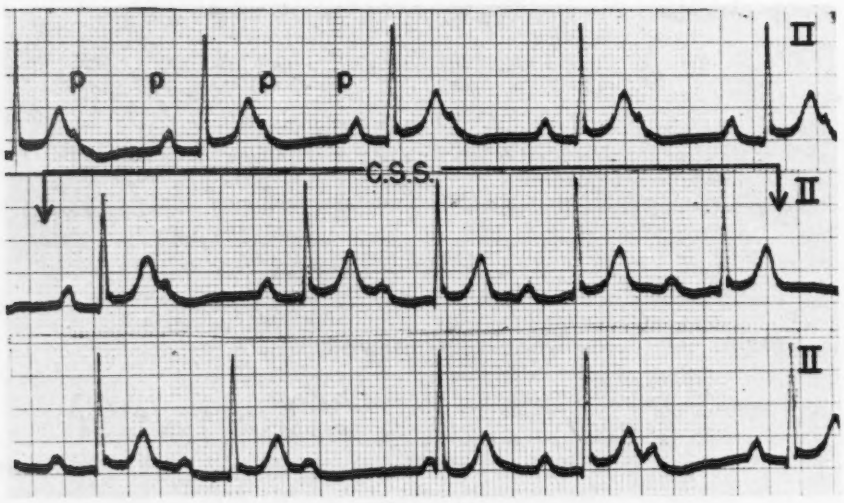

Figure 1

Acceleration of ventricular rate by carotid sinus stimulation (CSS). Continuous tracing. Upper strip shows 2:1 A-V block, A. rate = 102; V. rate = 51. Second and third strip during and after CSS when atrial rate was reduced to 68, a 1:1 response occurs.

retired workers the average fall in systolic pressure was 37 mm. Hg, whereas in 106 healthy soldiers it was only only 5 mm. Hg. The fall in blood pressure generally lasted several minutes and usually persisted longer than the bradycardia. There appeared to be no correlation between the degree of cardiac slowing and the extent of hypotension.

The basis for the fall in systemic pressure in man is probably vasodilatation in the splanchnic, renal, muscular, and cutaneous arterial circulations. Barcroft and Edholm[42] found considerable vasodilatation in the muscles of the forearm in a patient with vasodepressor syncope. The vasodilatation was annuled by sympathectomy of the limb, but not by a dose of atropine that prevented bradycardia.

The reflex effects upon the heart and peripheral vessels are independent of each other although they generally occur together. Atropinization abolishes rate changes but does not prevent reduction in blood pressure.

The Technic and Hazards of Carotid Sinus Stimulation

There are certain points of importance in the technic of stimulating the carotid sinus. With the exception of patients who are being tested for relief of anginal pain it seems best to have the patient recumbent in order to reduce the likelihood of syncope. The head is tilted either forward or backward, to one side or the other, until the expansile body is readily palpated. If the neck muscles are too taut or too slack, it is difficult to feel the appropriate part of the vessel. The sinus is usually situated just below the angle of the jaw at the upper level of the thyroid cartilage. The carotid bulb is massaged with pressure directed posteriorly and medially, the artery and sinus being compressed against the vertebral spine. Massage is applied for not more than 5 seconds at a time. Carotid blood flow is interrupted only transiently. The procedure may be repeated after several seconds.

The dangers of carotid sinus stimulation are believed to be due either to production of prolonged cardiac asystole or interference with cerebral circulation. Transient ventricular fibrillation has also been reported during carotid sinus pressure.[43] Review of the electrocardiograms in the one published case shows the ventricular fibrillation to have been a misinterpretation. The presumed arrhyth-

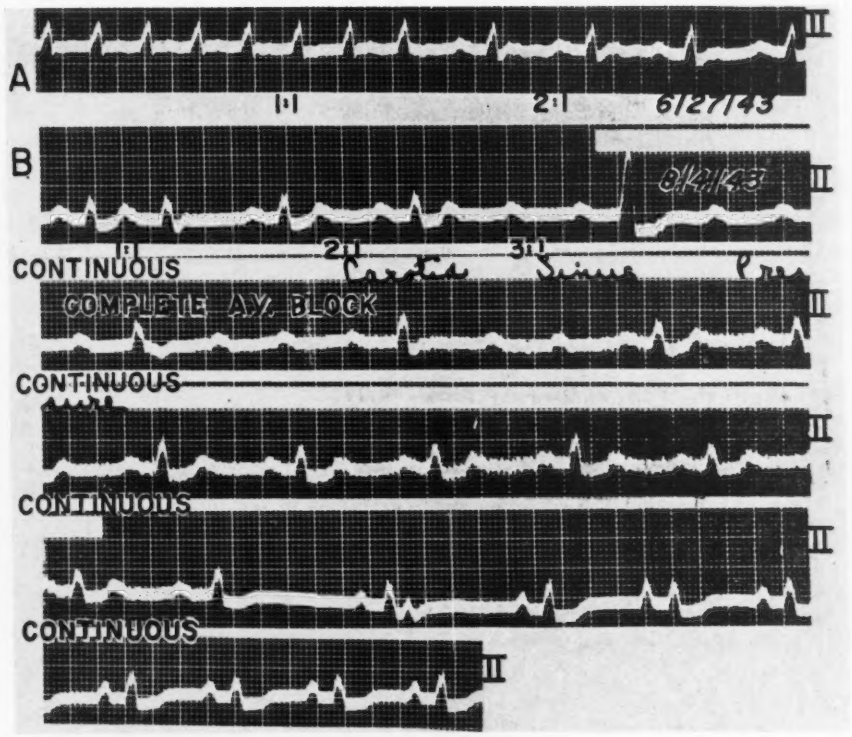

Figure 2

Paroxysmal atrial tachycardia with block (PAT with block) reverted to normal sinus rhythm by CSS (note signal). Stimulation probably started before signal and continued longer than generally advisable. Upper strip shows PAT with 1:1 and later with 2:1 response. Lower two strips show sinus rhythm.

mia was actually an artifact, the result of muscle tremor. In fact, permanent cessation of the heart beat or serious ventricular arrhythmias are almost unheard of. We are aware of only one fatality from a cardiac mechanism due to carotid sinus stimulation. This occurred in a 75-year-old man in whom the left carotid sinus was massaged to control a paroxysm of rapid heart action. The arrhythmia stopped but the heart beat was not resumed.[44]

A number of reports document the potentially harmful cerebral consequences of carotid sinus pressure.[45–48] Askey[45] described seven patients who developed hemiplegia with the cerebral lesion homolateral to the side of stimulation. In two patients no cardiac slowing developed. Two other instances of paresis or death are recorded.[46, 47] One is led to the conclusion that arrest of the carotid circulation resulting from prolonged compression of this vessel probably injured a portion of the brain already vulnerable. This view is supported by the fact that several of the patients had carotid artery insufficiency. On careful consideration it is evident that these complications were not an inherent part of the carotid sinus reflex. They were in fact the consequence of prolonged compression of the carotid artery and mechanical interference with cerebral blood flow.

In the light of the frequency of this maneuver and the few untoward reactions reported, risk of carotid sinus manipulation must be regarded as extremely small. A number of observers who have employed this test

extensively over many years have encountered no serious complications.[17, 49, 50] The present authors in an experience of several thousand such tests have noted but one brief episode of facial weakness which cleared in several minutes.

It has been our practice to limit the duration of each gentle massage to a time not exceeding 5 seconds. Bilateral occlusion is never carried out. Prior to the maneuver the carotid arteries should be auscultated for murmurs. Elderly patients, over 75 years of age, are generally not tested. Similarly in the presence of cerebral vascular disease, unless there are very pertinent indications, this maneuver is avoided. In such individuals there is not only the hazard of sclerosed and narrowed cerebral vessels but the reflex may be unduly sensitive with resultant prolonged asystole. This is especially prone to occur when carotid sinus stimulation abolishes a paroxysm of rapid heart action. In such an instance the tachycardia has depressed the sinus as well as subsidiary cardiac pacemakers. In the elderly individual, as was true in the experience cited above, it may lead to fatality. Ideally an electric cardiac pacemaker should be at hand, especially when the carotid sinus is stimulated in older patients.

During the carotid test the heart is listened to or the electrocardiogram is continuously observed. In patients with coronary artery disease or angina pectoris initial pressure is especially brief and gentle. As soon as the desired effect is obtained, the manipulation is stopped. Patients are generally in a sitting or recumbent position. If the above enumerated safeguards are followed the procedure is reasonably safe.

Clinical Applications

Arrhythmias and Carotid Sinus Pressure

Probably the greatest clinical value of carotid sinus stimulation is in the deciphering of cardiac arrhythmias. This procedure frequently enables the physician to make a definitive bedside diagnosis of the underlying mechanism. At times even after recording the electrocardiogram the nature of the disordered rhythm remains unclear until the heart rate or rhythm has been upset by this vagal maneuver. Carotid sinus stimulation is also an effective therapeutic tool in reverting both atrial and nodal tachycardia to a normal mechanism.

The carotid sinus test may be helpful at the bedside at all heart rates. When the rate is slow (between 30 and 50) and regular, one of three rhythms may be present: sinus bradycardia, 2:1 A-V heart block, and complete heart block. Carotid sinus massage permits differentiation among them. If the slow rate is unaffected by the carotid sinus test, the mechanism is likely to be complete heart block. If a smooth slowing results followed by a gradual resumption of the original rate, the rhythm is sinus bradycardia. When the slowing or reacceleration is irregular or jerky, the mechanism is partial heart block. Bedside confirmation of the presence of block, partial or complete, is provided by the detection of atrial sounds and the presence of a jugular "a" wave during diastole. An additional clue to 2:1 block is paradoxic acceleration of the ventricular rate during carotid sinus stimulation (fig. 1). With the vagal-induced slowing in atrial rate, the previously blocked impulse reaches the A-V node when it is no longer refractory to conduction, so that 1:1 atrioventricular response is established at a faster ventricular rate.

Ordinarily when the heart rate is found to be about 70 and regular, it is naturally assumed that a normal sinus mechanism is present. If for any reason one suspects an abnormality, however, carotid sinus stimulation may uncover the arrhythmia. If this test results in an abrupt slowing or halving of the rate with a jerky return to 70, the mechanism is not sinus rhythm but rather atrial flutter or paroxysmal atrial tachycardia with block. This suspicion may then be quickly confirmed if a brief effort exactly doubles the heart rate. Differentiation between the two can then be made by additional clinical study.

When the heart rate is rapid, between 120 and 300, and regular, the possible mechanisms

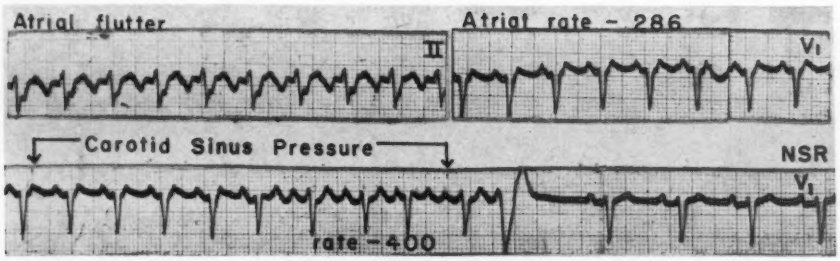

Figure 3

Atrial flutter reverted to normal sinus rhythm by CSS. Upper strip shows classical atrial flutter. Lower strip shows acceleration of atrial rate with CSS from 286 to 400 with abrupt termination of arrhythmia.

are sinus tachycardia, paroxysmal atrial or nodal tachycardia, paroxysmal atrial tachycardia with block, atrial flutter, and ventricular tachycardia. Carotid sinus stimulation is often decisive in establishing a diagnosis. If this maneuver abruptly stops the tachycardia and the rhythm remains slow and regular, one is dealing in the great majority of instances with paroxysmal atrial or nodal tachycardia. If carotid stimulation temporarily slows the ventricular rate, one can be quite certain that the arrhythmia is not classical atrial tachycardia or ventricular tachycardia. If the slowing is smooth and gradual with a similar return to the original rate, the mechanism is sinus tachycardia. If recovery from the temporary slowing is jerky with variation in duration of consecutive cycles, the mechanism is either atrial flutter or paroxysmal atrial tachycardia (PAT) with block. If the rate is unaltered, no decision can be reached concerning the rhythm. As a most unusual occurrence, carotid sinus stimulation may actually arrest such arrhythmias as PAT with block, atrial flutter or fibrillation and restore a sinus mechanism either temporarily or permanently (figs. 2 to 4).

When the rate is rapid and irregular, the common mechanisms one has to consider are multiple premature beats (especially atrial) with varying coupling, atrial fibrillation, atrial flutter, paroxysmal atrial tachycardia with block, and ventricular tachycardia. Slowing of the heart rate by the carotid sinus excludes ventricular tachycardia. If the slowed heart rate is regular, atrial fibrillation is excluded. If the heart slows, but the rhythm is irregular and exercise accelerates and regularizes it, one is dealing with atrial flutter, frequent premature beats or PAT with block.

Apart from these simple auscultatory observations at the bedside, electrocardiographic data can be obtained during carotid sinus manipulation, which establishes the presence or the nature of an arrhythmia that cannot be otherwise diagnosed.

Occasionally, with a slow ventricular rate and apparent 2:1 heart block, carotid sinus massage may slow the atrial rate without affecting the ventricular response. This would establish the presence of complete heart block and synchronization of atrial and ventricular pacemakers. The presence of an arrhythmia may be overlooked when the electrocardiogram reveals only one P wave before each QRS complex with a heart rate of 70 to 80. Suspicion of the presence of an arrhythmia is aroused under certain circumstances. One may detect a difference in the appearance of the P wave compared with its form in previous tracings, or the T wave may exhibit a small deformity not previously present, raising the possibility of a nonconducted P wave. Carotid sinus stimulation, by slowing the ventricular rate may dislodge a nonconducted P wave from its concealed location within the ventricular complex (fig. 5). This may provide the first and only proof of the

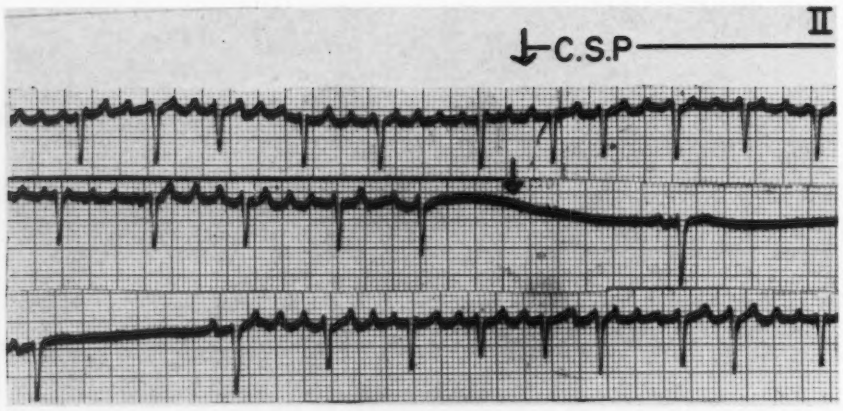

Figure 4

Temporary reversion from coarse fibrillation or impure flutter to normal sinus rhythm by CSS. This phenomenon could be reproduced repeatedly.

existence of PAT with block, a commonly overlooked arrhythmia, generally resulting from serious digitalis intoxication.

It is quite common to see tracings in which the ventricular rate is rapid, from 120 to 180, regular and with only one P wave evident. These electrocardiograms are often interpreted as instances of either normal sinus tachycardia or paroxysmal atrial tachycardia. The sharp and triangular P wave in lead II should, however, suggest atrial flutter. This is confirmed when carotid sinus massage increases the A-V block and reveals the typical saw-toothed undulation of atrial flutter. If, however, this procedure reveals an isoelectric baseline between P waves discharging at a rate of 120 to 220 while the ventricular rate is slowed, one is dealing with PAT with block (figs. 6 and 7).

At times, one encounters an arrhythmia with an atrial rate in the vicinity of 240 with atrioventricular block. The question then arises whether this is due to atrial flutter or PAT with block. If carotid sinus stimulation results in acceleration of atrial rate, the underlying mechanism is atrial flutter; such a response is, however, not the rule in flutter.

If one observes a regular or irregular rapid ventricular rate with a prolonged and deformed QRS complex, identification of the arrhythmia is difficult. The relation between atrial and ventricular activity must be established. Such a mechanism may be the result of a ventricular or supraventricular pacemaker, the latter complicated either by bundle-branch or intraventricular block. Carotid sinus stimulation is helpful, if atrial activity can be detected. If the atrial rate is slowed, but the ventricular rate is unaffected, A-V dissociation is present (fig. 8). One is then dealing with ventricular tachycardia, though rarely the mechanism may be nodal tachycardia complicated by retrograde block and impaired ventricular conduction.

Carotid sinus stimulation is also useful in the analysis of various symptoms. For example, if a patient complains of fluttering in the neck or chest and the electrocardiogram is normal, the physician can only guess the basis for these complaints. However, if carotid sinus pressure brings out anomalous A-V conduction, the symptoms probably are due to paroxysmal rapid heart action. In the patient with Wolff-Parkinson-White syndrome, reflex vagus stimulation impairs conduction in the normal A-V pathways, thus favoring impulse propagation through the accessory bundle. Still another problem is posed by the patient who complains of palpitation when the electrocardiogram shows no arrhythmia. It is then uncertain whether the difficulty is psychologic or due to an arrhythmia. If there

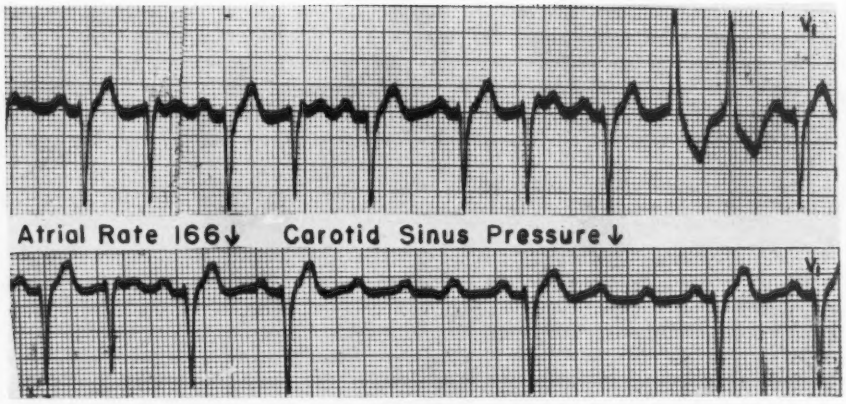

Figure 5

CSS uncovers P waves blocked in the ventricular complex. Upper strip resembles normal sinus rhythm, atrial flutter, or atrial fibrillation with ventricular ectopic beats. Lower strip shows PAT with block with atrial rate of 166.

is an arrhythmia, is it due to A-V block or ectopic beats; if ectopic beats are present, do they originate in the atrium, node, or ventricles? Carotid sinus stimulation frequently provides otherwise unobtainable information. In the patient with sporadic partial heart block, this vagal maneuver may reproduce the conduction defect. In the patient with recurring extrasystoles carotid sinus stimulation may bring the ectopic pacemaker to the fore (fig. 9).

It is clear from this discussion that an electrocardiogram obtained during carotid sinus stimulation is often the only means for identifying the mechanism of a cardiac arrhythmia. When a patient shows a rhythm disorder that is not readily deciphered, complete investigation requires determination of the response of the heart to vagal stimulation. Carotid sinus massage is usually the simplest and safest way of achieving this.

Angina Pectoris and Carotid Sinus Pressure

Angina pectoris is a distinct clinical entity. It is a painful subjective manifestation of a diseased coronary arterial system. The recognition of angina pectoris depends entirely upon the proper interpretation of symptoms. Frequently anginal pain is the only indication of ischemic heart disease. While the story is distinctive in the majority of patients, there are many with atypical aspects to this subjective experience. Furthermore, chest pain that simulates the anginal episode in one or more respects may not be due to coronary artery insufficiency, or for that matter, to any sort of heart disease. Any simple procedure that helps in distinguishing anginal pain from other chest discomforts is obviously of great value. Carotid sinus massage frequently provides critical information about the nature of the chest pain. At times this procedure affords relief that cannot readily be obtained by other means.

Wassermann, in 1928, was the first to point out that carotid sinus pressure may relieve anginal pain.[15] This observation has been amply confirmed.[51–56] The diagnostic and therapeutic implications of Wassermann's observation have been ignored by clinicians. Three of the leading current textbooks in cardiology do not even mention this subject.[57–59] Over the past 15 years, we have employed this technic in many hundreds of patients.[60, 61] Our continuing experience confirms the value of carotid sinus stimulation in the diagnosis of angina pectoris.

When a patient has chest pain, the physician should promptly listen to the heart. The stethoscope is best held in place by an attendant or by the patient when no one else is

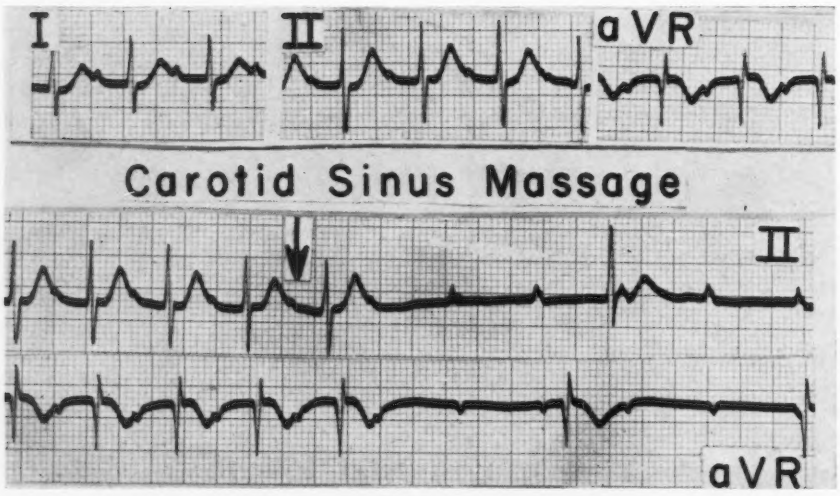

Figure 6

Mechanism regarded as sinus tachycardia (upper tracing). However, CSS induced atrioventricular block without a change in atrial rate, indicating presence of atrial arrhythmia.

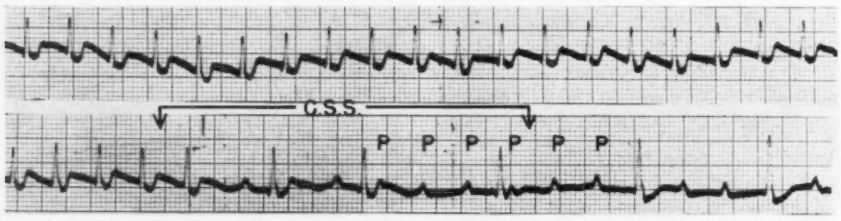

Figure 7

CSS uncovers PAT with block. Upper strip shows regular rhythm with rate of 170. Atrial impulse difficult to discern. Electrocardiogram resembles atrial flutter. Note CSS uncovers PAT with block with classical P waves.

available. Both hands are then free to perform the test. This maneuver is more effective if carried out with the patient in the sitting position. Coronary artery pain is usually less pronounced in the sitting than recumbent position. Just before the test, it is important to establish that the pain is still present. The right carotid sinus is first massaged; if this does not produce appreciable cardiac slowing, the left side is tried. The patient is then asked whether *the pain has become worse.* If the heart has been slowed, the patient with angina pectoris behaves frequently in a characteristic fashion: there is a pause before the answer is given, frequently with a look of uncertainty and puzzlement, "No, doctor, the pain is all gone"; or "it is letting up." Disappearance or lessening of the pain occurs almost instantly, within several seconds after the onset of slowing of the heart. Though the heart may promptly reaccelerate, generally the pain does not recur.

Of importance in the proper performance of the test is the exact wording of the question. The objective is to mislead the patient by suggesting that this maneuver has aggravated the chest discomfort. If, despite this deliberate misdirection, the patient says the pain is lessened or has disappeared, one can be certain that the subjective change is real and has not been suggested by the examiner. Pressure on the common carotid artery, below

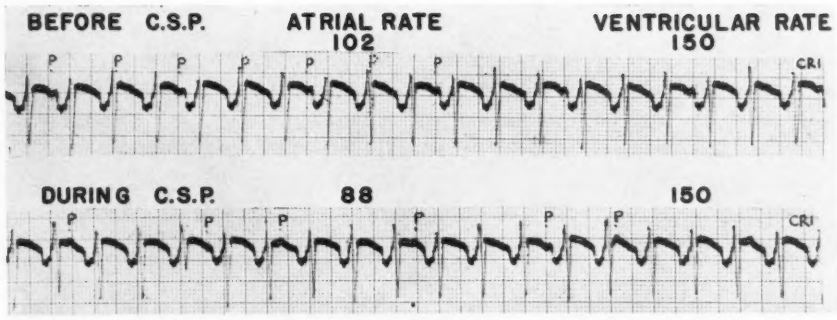

Figure 8

CSS slows atria but not ventricles thus establishing presence of atrioventricular dissociation, supporting the diagnosis of ventricular tachycardia. The QRS measures 0.16 second. Note atrial slowing from 102 to 88 while ventricular rate is unaffected.

the carotid bulb, at the angle of the mandible, or upon the sternocleidomastoid muscle, is without effect on the duration or character of the anginal attack. The lessening or control of angina pectoris is therefore not due to distraction by the introduction of another painful stimulus.

Our experience indicates that abolition of angina pectoris is almost invariably associated with slowing of the heart rate. In only one patient out of many hundreds was there relief of pain without slowing. This patient was experiencing a prolonged episode of substernal pain during an episode of supraventricular tachycardia. Carotid sinus pressure consistently relieved the pain though the rate was unaltered. When the pressure was stopped the pain returned. Freedberg and Riseman[62] have reported relief from pain in three of 13 patients without apparent change in heart rate. They found no relationship between the degree of cardiac slowing and the relief of cardiac pain. In one patient the heart rate was reduced from 115 to 56, yet there was no effect upon the anginal discomfort. These observers studied patients whose anginal pain was brought on by exercise in a cold room. Our observations have been made exclusively in patients with spontaneously occurring attacks.

We interpret this test in the following way: if an attack of chest pain is relieved by carotid sinus stimulation, we conclude that angina pectoris is present. If there is no relief or the pain is made worse, though the heart rate is slowed, the discomfort is not anginal in nature. The pain may still be due to coronary artery disease; however, in such an instance coronary insufficiency or thrombosis is the likely pathogenic factor. If heart rate does not slow, the test is regarded as inconclusive. In patients with functional chest discomforts, carotid sinus stimulation will frequently make the pain worse because of the suggestion by the physician. Occasionally the pain lessens transiently when good slowing is obtained during an actual acute myocardial infarction. Pain derived from gallbladder disease, hiatus hernia, cervical arthritis, or various other chest conditions generally is not relieved by this maneuver. Carotid sinus pressure is therefore a helpful diagnostic procedure in the analysis of chest pain.

Carotid sinus stimulation carried out during an episode of angina pectoris does not alter the ischemic electrocardiographic pattern nor does it abbreviate the duration of such S-T and T-wave changes even though the pain is relieved (fig. 10). During an exercise test the anginal pain may be totally prevented by massage of the carotid sinus, though S-T depression nonetheless occurs.

At present the mechanism of the relief of angina by carotid sinus massage is not clear. Acetylocholine in all concentrations dilates

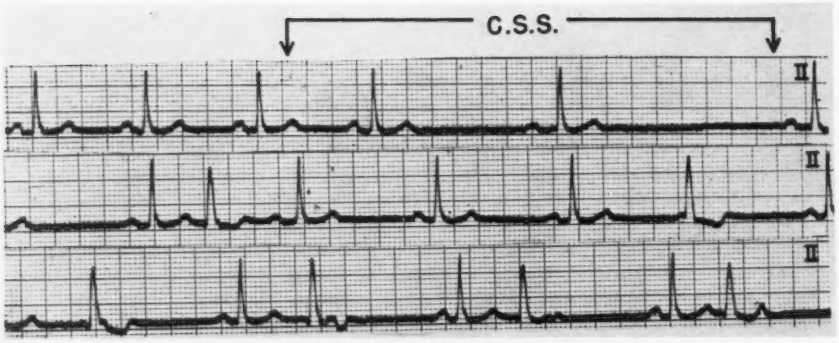

Figure 9

CSS reveals ventricular extrasystoles thereby explaining cause of palpitation in this case.

the coronary arteries.[63] However, in the presence of coronary atherosclerosis it has been suggested that coronary artery blood flow is fixed.[64] The facts that the electrocardiogram is not improved, that there may not be any slowing, and that the report of the relief of pain is only on the stimulated side have led some to the view that the effect is due to an interruption of a homolateral sympathetic reflex arc or sensory pathway from the heart.[63] Bronk and co-workers[28] have found that increase in carotid endosinus pressure diminishes tonic sympathetic discharge from the stellate ganglion. In extensive experience we have observed that pressure on the carotid sinus on one side is effective in relieving pain on both sides of the body. Left-sided arm pain is readily ameliorated by right-sided carotid sinus stimulation as well as the converse. Indeed, Bronk noted that distention of either carotid sinus produced inhibition of cardiac sympathetic impulses from both stellate ganglia.[28] If the mechanism were indeed transient sympathetic block in the sensory sympathetic pathways, i.e., in the perception of pain, it would be hard to account for the increased exercise capacity following such stimulation. Since slowing of the heart is so constantly associated with relief, one is tempted to ascribe the relief to the bradycardia. Is it not possible that with slowing in rate, there is less production and increased "'washing out" of an irritating catabolite responsible for the pain? An alternate explanation is that this reflex by its enhanced vagal and diminished sympathetic nerve action alters myocardial or vascular metabolism, diminishing the discrepancy between blood flow and requirement.

Coronary Artery Disease

A majority of patients with coronary artery disease exhibit increased carotid sinus sensitivity.[65, 66] Such enhanced responsiveness is more likely to be present during an acute myocardial infarction. About half the patients who experience angina pectoris have increased responsiveness, which is more marked during an episode of pain. Braun and Samet[67] have shown experimentally in cats that the effect of carotid sinus pressure was greatly increased when branches of the left coronary arterial system were tied.

In our experience the patient with coronary artery disease is especially prone to develop asystole after brief carotid sinus massage. This results from several factors: depression of the sinoatrial node, atrioventricular block, and delayed nodal or ventricular escape. Advanced degrees of heart block are prominent manifestations. Generally carotid sinus sensitivity varies directly with the degree of coronary artery disease and with the individual's age. We have diagnosed coronary artery disease in patients in their late thirties and early forties who complained of atypical chest pain, exhibited nonspecific alterations in S-T and T-wave complex but responded to mild and brief carotid sinus stimulation with partial or complete heart block.

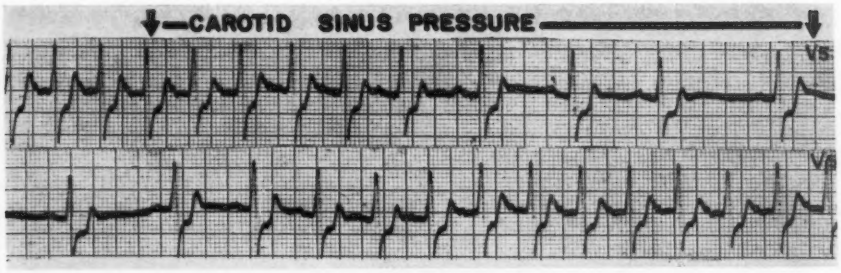

Figure 10

CSS relieved anginal pain brought on by a two-step test and slowed the heart transiently but did not alter the electrocardiographic S-T depression.

The carotid sinus test may be helpful in yet another way in establishing the diagnosis of coronary artery disease. When an electrocardiogram is recorded during this maneuver and slowing occurs, it is important to examine the T waves for a change in contour. If in the complex immediately following the longest pause, the T wave has become inverted but the QRS complex remains unaltered, myocardial disease is present. It has the same clinical significance as the postextrasystolic T-wave change, which has been ascribed to myocardial ischemia, generally the result of underlying coronary artery disease.[68] The similarity in T-wave alteration following an ectopic beat and brief cartoid sinus massage in a patient with coronary artery disease is illustrated in figure 11.

Carotid Sinus Stimulation in Acute Pulmonary Edema

Massage of the carotid sinus may relieve acute pulmonary edema in patients with hypertensive and coronary artery disease. This phenomenon was first noted by Wassermann.[16, 69] Alzamora-Castro and co-workers[70] found the maneuver to be effective in 80 per cent of patients with pulmonary edema. Relief is immediate and coincides with the onset of bradycardia. In the majority it is associated with a drop in blood pressure. The patient is promptly able to lie flat. Fear, dyspnea, and chest oppression disappear, perspiration lessens, and pallor vanishes. Pulmonary rales decrease or clear entirely, respirations become less labored, heart sounds diminish in intensity, and the apex impulse becomes less forceful. The episode frequently is completely reversed. If it recurs, it may be controlled for as long as carotid sinus stimulation is continued. When the reflex becomes exhausted on one side, a good response may be achieved by stimulating the opposite side. Such massage has been carried out for as long as 30 minutes.[70] A great advantage of the procedure is that the physician can control the changes in heart rate and blood pressure by varying the duration and intensity of stimulation. In the presence of atrial fibrillation or aortic valvular disease this maneuver has been unsuccessful in controlling acute pulmonary edema.

Carotid sinus stimulation will reduce the period of fatigue and the objective manifestations of cardiac overload in patients with heart disease undergoing exercise tests. Slowing of the heart rate with improved left ventricular efficiency as well as lowered peripheral resistance with reduced myocardial pressure work has been offered as the explanation for the salutory effects of carotid sinus massage in the presence of acute left ventricular failure.[70] Wassermann,[69] however, believed that acute pulmonary edema is not due to backward failure of the left ventricle, but represents a reflex syndrome involving the cardiopulmonary segments of the autonomic nervous system. The prompt relief provided a morphine, a powerful depressant of the central nervous system with affinities for the respiratory and vasomotor centers, supports

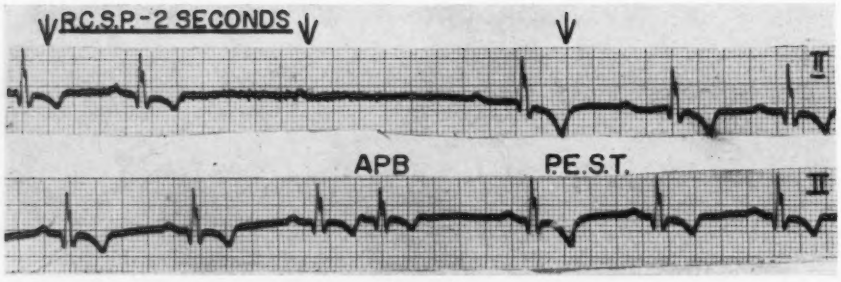

Figure 11

Accentuation of inverted T wave following a pause produced by CSS. Note similarity of this effect to postextrasystolic accentuation of T-wave inversion.

this view. Acute pulmonary edema begins with tachycardia, elevation of blood pressure, cutaneous vasoconstriction, and other sympathetic manifestations. These may be due to decreased baroreceptor activity that would be reversed by carotid sinus stimulation. Wassermann[69] has suggested that angina pectoris and paroxysmal pulmonary edema are initiated by a common afferent reflex pathway residing in the coronary artery nervi vasorum. A number of clinical observations may be pertinent in this context. Both angina pectoris and acute pulmonary edema are helped by carotid sinus massage and nitroglycerin. Angina pectoris and chronic atrial fibrillation infrequently coexist. Similarly, acute paroxysmal pulmonary edema is rare in the presence of established atrial fibrillation; when it does occur, carotid sinus stimulation is without effect.

These observations are of considerable theoretical and practical importance. The effectiveness of carotid sinus stimulation in the treatment of pulmonary edema needs further clinical elaboration.

Carotid Sinus Pressure and Bundle-Branch Block

Left bundle-branch block makes the electrocardiographic recognition of fresh or even old myocardial infarction difficult or impossible. Slowing of the ventricular rate with carotid sinus massage may temporarily abolish the block and permit analysis of the basic ventricular complex. The presence or absence of an infarction pattern can then be readily observed. It is reasonable to assume that in the evolution of bundle-branch block, there exists a phase of conduction impairment that will be affected by a change in heart rate. Rate-conditioned variability in conduction is especially likely to be present at the onset of bundle-branch block. At such times carotid sinus induced slowing of the heart proves helpful in determining whether or not bundle-branch block is associated with other electrocardiographic abnormalities. Reflex vagal stimulation may temporarily restore normal intraventricular conduction even without a change in heart rate.[71]

The following brief case report—one of a number of similar experiences—illustrates this problem.

The patient, a 53-year-old woman with rheumatic aortic valvular disease and heart failure, was found to have left bundle-branch block. The possibility of an acute myocardial infarction could not be ruled out. It was noted, however, that normal conduction for one or more beats occurred when the heart rate was slowed by means of carotid sinus stimulation. Brief massage was therefore carried out as each lead was recorded. The normally conducted complexes were found to be essentially unaltered when compared with earlier tracings taken prior to this episode (fig. 12).

Carotid sinus stimulation during auscultation of the heart occasionally helps in the recognition of unsuspected left bundle-branch block. When this vagal maneuver results in an abrupt increase in the intensity of a muffled and reduplicated first heart sound with but slight reduction in heart rate, bundle-branch block may be considered. The explanation for this auscultatory phenomenon is

that with development of left bundle-branch block, the interval between atrial and left ventricular systole is lengthened, resulting in a decreased first sound at the apex. With the temporary establishment of normal conduction, the interval between atrial and left ventricular systole becomes shorter, with a resultant louder first heart sound. This is comparable to the well-known alteration of the first sound that follows changes in the P-R interval.

Digitalis and the Carotid Sinus Reflex

It is well established that digitalization may sensitize the heart to carotid sinus stimulation. The enhanced vagal response to carotid sinus massage results in greater slowing, cardiac standstill, or complex arrhythmias (fig. 13). As little as 0.2 Gm. of digitalis leaf has been reported to produce increased carotid sinus sensitivity in man.[72] At times such sensitivity occasions bizarre problems. For example, one patient complained of being periodically "abstracted." He found it difficult to elaborate upon this symptom, and despite much questioning no further light could be shed on the meaning of this term. This very sensation of "abstractness" as well as prolonged cardiac standstill was reproduced by brief massage of the carotid sinus. After digitalis therapy was stopped, carotid sinus stimulation no longer induced symptoms or cardiac standstill.

The increased cardiac response to carotid sinus massage that follows digitalization can be utilized in the treatment of supraventricular tachycardia. When this vagal maneuver fails to arrest classical atrial tachycardia, it may still be effective if performed after digitalis administration. Our practice has been to massage the carotid sinus before each additional increment of digitalis is administered. A smaller dose of drug is then required for restoration of normal rhythm. The likelihood of digitalis intoxication is thereby diminshed.

Carotid sinus stimulation occasionally provides the earliest evidence of digitalis intoxication and clarifies unusual and hitherto unexplained symptoms. The following experience is illustrative. A patient was bedridden with intractable vertigo. He had no other complaints. Neurologic examination was essentially negative. He denied taking digitalis. When carotid sinus stimulation was carried out, he exhibited Wenckebach type of A-V conduction disturbance. He was therefore advised to bring in all of his medications. It was found that he was taking 0.2 mg. of digitoxin daily, though he was unaware of the name or the nature of this medicine. Symptoms promptly disappeared on stopping the digitoxin.

The possibility of digitalis intoxication needs to be considered in any digitalized patient who develops advanced degrees of heart block during carotid sinus stimulation, especially when this response was absent previously. The emergence of rapid and regular ventricular response in the patient with atrial fibrillation after carotid sinus stimulation has similar implications. Likewise the development of ectopic beats or fixed coupling during this test provides the earliest evidence of digitalis overdosage (fig. 14). In fact, carotid sinus massage will permit the recognition of disorders of rhythm due to overdigitalization before they occur spontaneously. In these patients without objective stigmata of digitalis overdosage, straining, excitement, or sudden cardiac overloads by either pressure, volume, or rate work may precipitate serious digitalis arrhythmias or even death. The lengthening of the cardiac cycle by carotid sinus stimulation favors discharge of a ventricular ectopic focus. The compensatory pause after a premature systole predisposes to fixed coupling. Langendorf and co-workers[73] have termed this phenomenon the "rule of bigeminy." Once bigeminy is initiated, it may persist for many minutes. The longer pause after each premature beat tends to sustain the mechanism. Furthermore, Scherf[74] has demonstrated that stimulating the vagus caused many ventricular extrasystoles and other ventricular arrhythmias in dogs who had received a cardiac irritant such as aconitine.

These experiences lead to the conclusion that carotid sinus stimulation should be em-

ployed more frequently in the process of digitalization. It is indicated in the patient who experiences symptoms suggestive of digitalis overdosage in the absence of any objective evidence of such a disorder. It is also of value during digitalization of patients suspected of having a low threshold to the toxic action of the cardiac glycosides. The maneuver may prove helpful in digitalized patients with heart failure presenting unexplained symptoms or signs.

Carotid Sinus Syndrome

Since Weiss and co-workers[17, 75, 76] first emphasized that a hypersensitive carotid sinus may be responsible for syncopal episodes, an extensive literature has accumulated on the so-called carotid sinus syndrome.[77–87]

The syndrome may be defined as the spontaneous occurrence of faintness or loss of consciousness that is reproducible by stimulation of the carotid sinus on either right or left side, but not by pressure upon the carotid vessels below the sinus. To make certain that the cerebral manifestations are not the result of obstruction of the carotid circulation, it is worthwhile to palpate the ipsilateral superficial temporal artery just in front of the ear during manipulation of the carotid sinus.[88, 89] Continued pulsation of this vessel would indicate that cerebral blood flow has not been critically obstructed. The syndrome is more readily produced with the patient either sitting or standing. The episode, whether occurring spontaneously or indeed deliberately, depends upon marked slowing of the heart rate, reduction in blood pressure, or both. Loss of consciousness usually lasts no more than several seconds and is usually preceded by such aurae as blurred vision, vertigo, tinnitus, faintness, visual hallucinations, and at times weakness, paresthesias, and even epigastric distress. Objectively the patient exhibits facial pallor, hyperpnea, and increased perspiration. The unconsciousness may be accompanied by convulsive phenomena, either focal motor or psychomotor. Abdominal cramps, diarrhea, and even angina pectoris have been ascribed to hyperactivity of the carotid sinus.[78, 90] Syncopal attacks due to carotid sinus sensitivity may be distinguished from seizures of other etiology by their predominant occurrence when the patient is standing, by their rapid onset and short duration, by the usually clear postictal sensorium, and by their reproduction on brief carotid sinus massage.[89, 91]

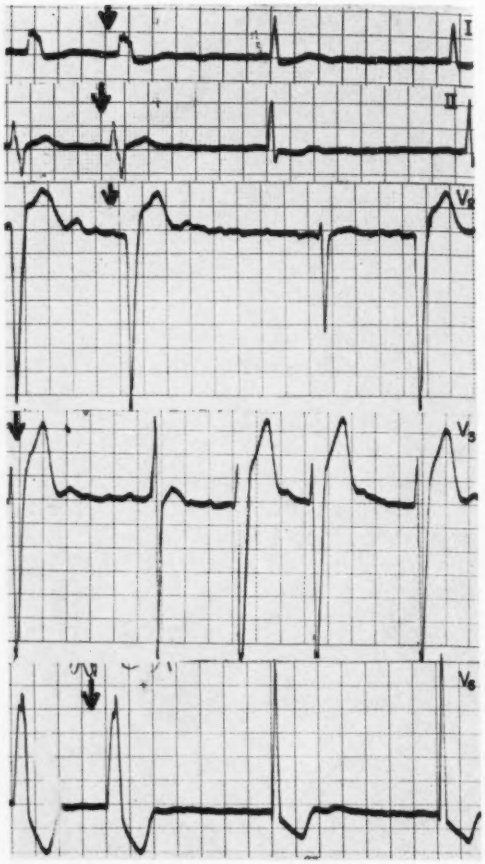

Figure 12

CSS (at arrow) by slowing the heart transiently permits normal conduction in each lead. This thereby reveals no evidence of myocardial infarction.

Attacks may be precipitated by any factor that exerts direct pressure or tension on the carotid sinus. The following have been implicated: tight collar, cervical gland, pressure over the area while shaving, sudden turning

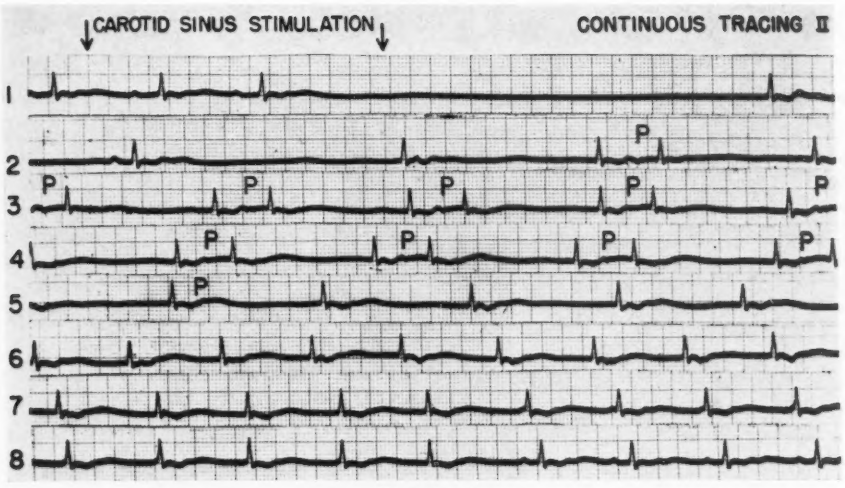

Figure 13

CSS produces prolonged asystole (5 seconds) and syncope in over-digitalized patient; this was followed by nodal and reciprocal rhythm. The entire arrhythmia lasted 58 seconds (continuous tracing). After discontinuation of digitalis, repetition of CSS was entirely negative.

of the head, coughing, straining at stool, or abrupt change from the supine to the erect position. A positive history of such associated factors is reported in only a quarter of the patients with this syndrome.[87] When carotid sinus sensitivity exists, it can usually be elicited on both sides, albeit to an unequal degree. It must be borne in mind that there are individuals in whom the carotid sinus is quite sensitive, even to the degree that massage will precipitate actual unconsciousness and yet no spontaneous symptoms may be present.

Syncopal attacks occur predominantly in men, and older age groups are favored. In 150 patients with carotid sinus-induced fainting spells, all were over 30 years of age and 70 per cent were between the ages of 50 and 70 years.[84] The majority of patients are afflicted with cardiovascular disease.[92] This syndrome, however, is not due to sensitization of the efferent outflow of the vagus as it enters the heart muscle. Stimulation of the distal end of the vagus does not reproduce the observed changes. Procainization of the vagus does not block this reflex. Furthermore, in careful studies by Weiss and Baker[17] of 15 patients with the cardio-inhibitory syndrome, nine had local pathology in the region of the sinus. In six it was due to aneurysmal dilatation of the carotid sinus, and in three to an adjoining tumor impinging upon the wall of the sinus. No gross pathologic findings were detected in the remaining six patients. In a later study,[75] of 52 patients, 31 had abnormalities in the region of the sinus wall. Thus sensitization of the afferent nerve endings within the carotid sinus accounts for the increased sensitivity to external pressure or internal tension.

Weiss and co-workers[93] distinguished three types of mechanism underlying this syndrome:

1. A cardio-inhibitory reflex consisting of prolonged ventricular asystole due either to complete A-V block or sinoatrial standstill without prompt ventricular escape. The mechanisms are prevented by atropine or epinephrine. This was observed in 34 per cent of 56 patients.

2. A vasodepressor reflex occurring independent of changes in heart rate and resulting from generalized vasodilatation with a

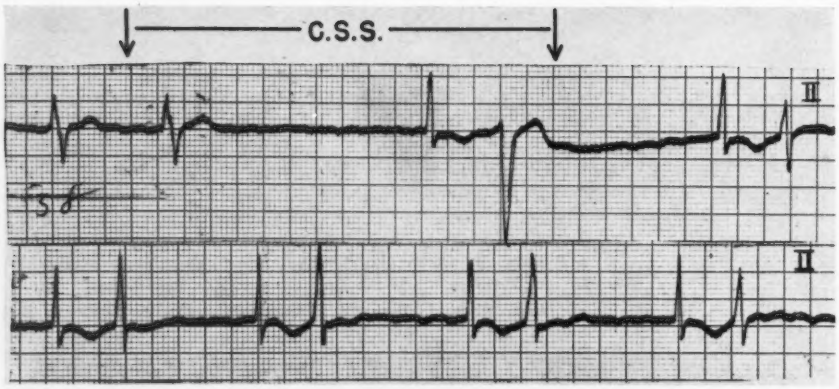

Figure 14

CSS reveals ventricular bigeminy as earliest definite evidence of digitalis intoxication.

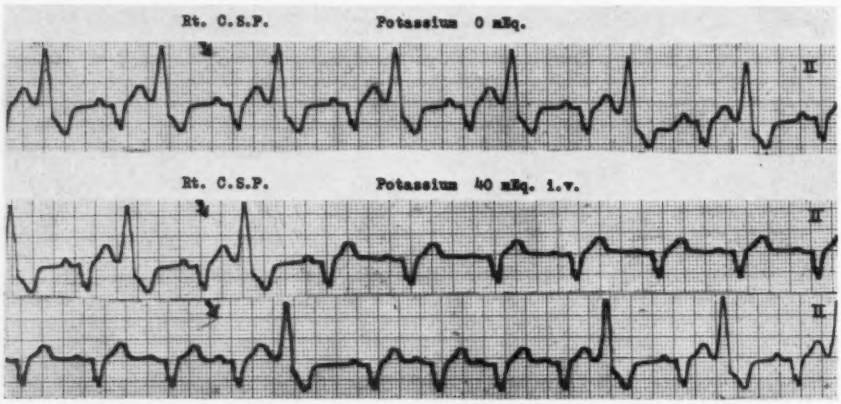

Figure 15

CSS following potassium administration abolishes ventricular bigeminy. Neither potassium infusion nor CSS alone was effective.

fall in blood pressure. It can be prevented by epinephrine or other sympathomimetic agents. Five per cent of patients with carotid sinus sensitivity exhibit this mechanism.

3. A "cerebral" reflex presumed to be due to vasoconstriction of cerebral blood vessels without changes in heart rate or blood pressure and not prevented by atropine or epinephrine. Loss of consciousness was ascribed to this mechanism in 60 per cent of the patients.[93]

We have never observed the cerebral type of this syndrome; our technic consists of transient massage of the carotid bulb. Ask-Upmark[94] first suggested that mechanical interference with blood flow in the carotid artery during sinus stimulation was responsible for the so-called cerebral type. In a study of 100 patients with hemiplegia or hemiparesis who reacted with syncope upon carotid compression, it was found that all those who did not develop bradycardia or a fall in blood pressure had occlusive vascular disease either in the opposite carotid, the anterior cerebral, or the basilar arteries demonstrable by angiography.[92]

A recent study by Toole[88] is instructive. In 17 patients who developed cerebral manifes-

tations upon compression of the carotid sinus, this syndrome could not be reproduced when the pressure was insufficient to obliterate pulsation in the ipsilateral distal temporal artery. In all but four of these reactors, a response identical with that obtained over the carotid sinus was elicited by similar compression of the common carotid artery, i.e., the effect was not specific for the sinus. Furthermore, when procaine was infiltrated into the sinus adventitia and the cervical sympathetics on the same side were blocked, carotid sinus compression was still effective in provoking cerebral manifestation. Arteriography or carotid surgery in 12 of the 17 demonstrated a markedly stenosed or occluded carotid on the side opposite to the sensitive vessel. It has been shown[95] that if one carotid is diseased, digital compression of the opposite vessel can produce a cerebral response simulating that occurring with the carotid sinus reflex. The evidence therefore suggests that a cerebral reflex is not elicited by carotid sinus stimulation. Syncopal attacks may be considered to be due to the depressor reflex when they are produced by massage requiring no more than 5 seconds of stimulation; however, when mechanical compression lasting 10 to 40 seconds produces these attacks the mechanism is due to occlusion of the underlying carotid artery.

Miscellaneous Considerations

The carotid sinus test may prove helpful during auscultation of the heart. There are times when it is difficult to distinguish the first from the second sound and to decide which is systole and which is diastole. This is most likely to occur when the rate is 120 or over and the two sounds are of equal intensity. Carotid sinus stimulation by slowing the heart rate, lengthens the diastolic interval. The sound following the longer diastolic pause is then easily identified as the first sound. A diastolic rumble of mitral stenosis may be heard only after slowing of the heart rate induced by carotid sinus effect.

A number of disease states are associated with altered sensitivity to carotid sinus stimulation. Conditions predisposing to sinus tachycardia are generally associated with diminished sensitivity or complete unresponsiveness. Most noteworthy are febrile states, anemia, thyrotoxicosis, acute cor pulmonale, and pneumonia. Increased sensitivity occurs in the elderly, in the presence of coronary artery disease, and in angina pectoris. Syncopal attacks and even convulsive episodes have been long known to occur with biliary colic. These may be due to the increase in carotid sinus sensitivity associated with gallbladder disease. In 23 patients with symptoms of acute biliary obstruction, 18, or 78 per cent, showed cardiac standstill lasting 3 or more seconds during massage of the carotid sinus.[96, 97] Following operation carotid sinus sensitivity disappeared in seven of 10 patients with liver disease in the absence of jaundice or common duct obstruction. It has been reported that sodium taurocholate or sodium glycocholate when injected into the common carotid artery or around the carotid sinus of dogs predisposes to bradycardia and hypotension.[98, 99] No such reaction resulted when the carotid sinuses were denervated or the vagi were sectioned. The bradycardia that accompanies jaundice may therefore be due to increased baroreceptor activity resulting from receptor sensitization by the retained bile pigments.

Increased carotid sinus responsiveness follows various drugs. In addition to the digitalis glycosides, cholinergic drugs may similarly increase the reactivity of this reflex. An important group of drugs that significantly increases carotid sinus sensitivity are the rauwolfia derivatives. Serious reaction may occur when large doses are employed in the digitalized patient. Unappreciated is the fact that potassium may enhance vagus action[100] and therefore increase responsiveness to carotid sinus stimulation. An example of this interaction is illustrated in figure 15.

Summary and Conclusion

The carotid sinuses, situated at the bifurcation of the common carotid arteries, are important pressoreceptors. They are activated by changes in pulsatile intravascular pressure, thereby initiating reflexes that modify heart

rate, cardiac output, blood pressure, peripheral resistance, and venomotor tone, as well as pulmonary blood flow and ventilation. Their superficial location in the neck permits ready manipulation and influence upon the heart and peripheral vessels.

Massage of the carotid sinus, when a few simple precautions are heeded, is a procedure devoid of serious hazard. This procedure had been much neglected. At times it affords the only means of establishing a definite diagnosis. Often it provides invaluable clues for diagnosis of various heart conditions and frequently serves as a definite therapeutic procedure. Carotid sinus stimulation is of value in diagnosis, treatment, or analysis of the following: arrhythmias of the heart, angina pectoris, coronary artery disease, acute pulmonary edema, bundle-branch block, and the state of digitalization. Increased sensitivity of the carotid sinuses may evoke reflexes that seriously impair heart rate, peripheral resistance, or both, and may thereby precipitate syncopal episodes.

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Each period of human achievement has its phases of spring, culmination, and decline, ... If we believe ourselves at last to have found the only thoroughfare, we owe this knowledge to those who before us travelled the uncharted seas. If we have inherited a great commerce and dominion of science it is because their argosies had been on the ocean, and their camels on the desert.—THOMAS CLIFFORD ALLBUTT, M.A., M.D. *Science and Medieval Thought,* London, C. J. Clay and Sons, 1901, p. 15.

ABSTRACTS

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PHARMACOLOGY

Chiche, P., and Pernot, J. M.: Study of Certain Paroxysms of Tachycardia during Treatment with Digitalis. Arch. mal. coeur. 53: 1 (Jan.), 1960.

The first patient, who was in severe congestive failure after myocardial infarction and was treated with mercurial diuretics and digitalis, developed paroxysms of regular tachycardia at a rate of 160, with poorly defined P waves and QRS complexes resembling right bundle-branch block. The serum potassium was normal. After withholding digitalis, sinus rhythm with a long P-R interval returned, but recurrence of heart failure again necessitated digitalis. This drug caused single, premature, wide QRS complexes of the same form as during the tachycardia. These complexes were followed by atrial tachycardia at the rate of 180, with variable 2:1 A-V block, then by tachycardia with a different form of the P wave and incomplete left bundle-branch block. In this patient a dose of digitalis necessary to prevent heart failure always caused these tachycardias. The second patient showed atrial fibrillation with congestive failure; diuretics and digitalis at first caused slowing of ventricular rate, then the appearance of regular wide QRS complexes resembling right bundle-branch block; hypotassemia was present at this time. Withdrawal of digitalis and treatment with potassium and procaine amide restored the slow irregular ventricular rate. This sequence was repeated after recurrence of failure, but this time procaine amide led to collapse and death, in spite of pressor agents. It is possible that the use of potassium together with digitalis could have prevented the toxic manifestations in these 2 patients. Withdrawal of digitalis and administration of potassium is an important step in their treatment although its effectiveness does not furnish direct proof of the role of potassium in their genesis. The third patient with mitral stenosis and acute pulmonary edema developed atrial tachycardia of 240 with variable A-V block after digitalis. Further digitalization increased the atrial rate to 300, resulting in the typical serrated configuration of atrial flutter with 2:1 conduction, and finally led to atrial fibrillation, which was converted to sinus rhythm with hydroquinidine. This patient demonstrated the difficulty in determining the role of digitalis in the etiology and graphic aspects of the tachycardia, while the first 2 patients emphasized the difficulty in the distinction between ventricular tachycardia and atrial tachycardia with ventricular aberration.

LEPESCHKIN

Ford, R. V.: Comparative Effects on Urinary Electrolyte Excretion Following Two Benzothiadiazine Diuretics, Flumethiazide and Chlorothiazide. Am. J. M. Sc. 239: 165 (Feb.), 1960.

Ten patients with mild edema were given single doses of 1 Gm. of chlorothiazide and 1 Gm. of flumethiazide at 5- to 7-day intervals after their

return to a control state. Observations were made on the 24-hour urinary output of sodium, potassium, bicarbonate, chloride, pH, and urine volume. There was a significant increase in potassium excretion with both drugs, which was somewhat less with flumethiazide. The increase in pH and bicarbonate excretion was less with flumethiazide. Because of this, flumethiazide may be said to promote a less complicated naturetic effect than does chlorothiazide, when the 2 drugs are given in equal doses. There was no significant difference in sodium, chloride, or urine volume.

SHEPS

Freeman, I., and Wexler, J.: Quinidine in Chronic Atrial Fibrillation. Am. J. M. Sc. **239:** 181 (Feb.), 1960.

One hundred unselected consecutive hospitalized patients with atrial fibrillation and cardiac decompensation were treated by bed rest, salt restriction, digitalization. and mercurial diuretics. This control group was compared with a subsequent series of 100 unselected patients admitted in the next 5 years and treated in the same manner with the addition of anticoagulants and quinidine. Oral anticoagulants were administered for 12 to 14 days prior to the administration of quinidine. Only 1 of the control group spontaneously reverted, whereas 57 of the treated group reverted. There were 18 deaths among the control subjects as compared to 1 in the treated group. Eleven of the control subjects were necropsied and 7 of these exhibited thromboembolic phenomena, which accounted for their deaths. There was a clinical suspicion of infarction in 3 of the remaining 7, who were not necropsied, and in 4 of the 82, who survived. There were no recognizable thromboembolic complications in the treated group. The cause of the single death in the treated group was intractable heart failure. Bundle-branch block and extreme cardiomegaly offered no particular obstacles to successful reversion. Ten patients were more completely compensated after reversion. On the basis of these observations the authors suggest that it is safe and desirable to use vigorous measures directed toward establishing normal sinus rhythm on all hospitalized patients with chronic atrial fibrillation.

SHEPS

Kitchin, A. H., Lloyd, S. M., and Pickford, M.: Some Actions of Oxytocin on the Cardiovascular System in Man. Clin. Sc. **18:** 399, 1959.

The cardiovascular effects of oxytocin were studied in 30 subjects by measuring hand and forearm blood flow, blood pressure, pulse, and cardiac output following a single injection or a continuous infusion of a synthetic oxytocin believed to be identical with the natural hormone. A drop in peripheral resistance was accompanied by an increase in hand and forearm blood flow, a drop in systolic and diastolic blood pressure, and tachycardia. Small intra-arterial doses of oxytocin produced consideration vasodilatation. The magnitude of the effect decreased with repeated injection. The effect was abolished by the addition of one twentieth the number of units of vasopressin.

KURLAND

Rodensky, P. L., Kathe, J. H., and Wasserman, F.: The Effect of Quinidine on Tolerance to Digoxin. Am. J. Cardiol. **5:** 498 (Apr.), 1960.

Three groups of nephrectomized, anesthetized dogs received respectively infusions of digoxin until ventricular fibrillation or standstill occurred, quinidine hydrochloride until greater than 25 per cent widening of the QRS complexes was observed, or quinidine until QRS widening was noted, then digoxin until ventricular fibrillation or standstill developed. The mean lethal dose of digoxin alone was 0.293 mg. per Kg., while after a large or lethal administration of quinidine the mean lethal digoxin dose was 0.275 mg. per Kg. The failure of quinidine to protect against digitalis-induced ectopic rhythms and its apparent reduction of digoxin tolerance in some dogs led the authors to conclude that the consequences of treatment of digitalis-generated arrhythmias with quinidine might be unpredictable or hazardous.

ROGERS

PHYSICAL SIGNS

Hallidie-Smith, K. A.: Some Auscultatory and Phonocardiographic Findings Observed in Early Infancy. Brit. M. J. **1:** 756 (Mar. 12), 1960.

Two hundred and thirty infants were examined daily from birth for a minimum of 8 days. Observations were made on heart rate, sounds, and murmurs. Twenty-five of this group were reexamined between the ages of 6 weeks and 6 months. Phonocardiograms were taken in about 25 per cent of the series before and after birth and also in a few patients with known congenital cardiac lesions. The mean sleeping heart rate showed a significant rise from the second to the eleventh day. All murmurs were systolic and the incidence increased with age, reaching 77 per cent by the eighth day and nearly 90 per cent at follow-up examinations. It is worth noting that in the normal infants no systolic murmurs were

loud, long, or high-pitched and no diastolic murmurs were audible. The majority of fetal tracings demonstrated systolic murmurs and hence, this chance observation does not necessarily imply congenital heart disease.

KRAUSE

PHYSIOLOGY

Bauereisen, E., Peiper, U., and Weigand, K. H.: Diastolic Suction of the Ventricles. Ztschr. Kreislaufforsch. **49**: 195, (Mar.), 1960.

An isolated frog heart can be emptied completely when a negative pressure of 10 mm. Hg is applied to the perfusion cannula, and starts to fill again when this pressure is reduced to 6 mm. The contracting heart, which is never completely empty, does not fill itself if the negative pressure in the ventricle exceeds 2 mm. of water, regardless of the rate of stimulation. However, at smaller negative or at positive pressures the filling is greater at low rates, since filling is a slow process. As the diastolic suction force depends on the ventricular volume, it is accentuated by all factors that increase the degree and force of systolic contraction. When ventricular filling against slight negative pressure was delayed until the end of diastole, the final ventricular volume for a given pressure was the same as when filling started immediately after the end of systole. This shows that the diastolic suction is not caused by an active force appearing during diastole but by passive elastic forces that receive their energy during systole.

LEPESCHKIN

Cairns, A. B., Jr., Love, W. D., and Burch, B. E.: The Effects of Acetyl-Strophanthidin on the Kinetics of Potassium and Rb^{86} in the Myocardium of Dogs. Am. Heart J. **59**: 404 (Mar.), 1960.

The kinetics of myocardial potassium were studied in dogs immediately following the administration of acetyl-strophanthidin. The technic utilized an Rb^{86} tracer. Immediately following the administration of acetyl-strophanthidin there was a loss of potassium from the myocardium that averaged 0.25 mEq. per Kg. of left ventricle per minute and a decrease in the extraction of Rb^{86} by the myocardium from the blood. Calculations indicated that the decreased extraction of Rb^{86} by the myocardium after acetyl-strophanthidin could be explained by a fall of 42 per cent in the flux of potassium across the myocardial capillary or by a doubling of the amount of plasma functionally shunted past myocardial capillaries.

SAGALL

Cudkowicz, L., Abelman, W. H., Levinson, G. E., Katznelson, G., and Jreissaty, R. M.: Bronchial Arterial Blood Flow. Clin. Sc. **19**: 1, 1960.

Bronchial blood flow can be measured indirectly from an estimate of the difference between the minute flows of the left and right ventricles. In this study the indirect values for bronchial arterial flow were calculated by the simultaneous recording of indicator-dilution curves from the pulmonary artery and a systemic artery after a single peripheral injection of dye. The values were compared with those attained from simultaneous indicator-dilution curves recorded from the left atrium and in a systemic artery after injection of dye into the ascending aorta, just distal to the coronary ostia. The values for bronchial flow by both methods for normal subjects indicated that it did not exceed 2 per cent of left ventricular output. Ligation of 1 pulmonary artery in dogs resulted in augmented values for bronchial flow varying from 15 to 31 per cent of left ventricular flow. Four of 6 patients with clubbing of the fingers showed increased bronchial flow by both methods.

KURLAND

Ellis, C. H.: Coexisting Mechanical and Electrical Alternation in Drug-induced Pulsus Alternans in Dogs. Am. J. Physiol. **198**: 327 (Feb.), 1960.

Alternation can be evoked in the dog heart by intravenous injections of moderately large doses of methoxamine hydrochloride. In a study of responses to 123 doses in 50 dogs, "true" pulsus alternans without measurable electrical alternation occurred most frequently. Coexisting electrical alternation was present in only one fourth of the cases in which mechanical alternans was induced by the drug. Only once did electrical alternans develop in the absence of mechanical alternans. Electrical alternation, when present, was usually limited to changes in the amplitude of the T wave and only rarely of the R wave. The usual pattern was one in which the electrogram associated with the weaker ventricular contraction showed greater negativity than that for the stronger heart beat. The mechanism of mechanical alternans is probably independent of that of electrical alternation. When T-wave changes are the only electrical evidence of alternation, beat-to-beat changes in time of onset of repolarization in localized areas of the myocardium are believed to be involved. Changes in the R wave indicate that conductional delays may play a role, but since alternation in the R wave was rare in drug-induced alternans, it is doubtful that delayed conduction is of great general significance.

KAYDEN

Goodyer, A. V. N., Chetrick, A., and Huvos, A.: Effect of Lanatoside-C on Cardiac Output. Yale J. Biol. & Med. **32**: 265 (Feb.), 1960.

Thirty subjects who had no clinical evidence of cardiac or respiratory impairment were studied at rest and during the fourth minute of exercise on a motor-driven treadmill set at a grade of 7 degrees and at a speed of 1.2 to 3.5 miles per hour. This exercise was representative of the more strenuous activity encountered by many of the subjects in their ordinary lives. Cardiac output was measured by an indicator-dilution method using an earpiece cuvette. Ratios of values of cardiac output at rest and during exercise were derived by direct comparisons of the areas of the dye curves recorded from each subject with a fixed earpiece placement and after repeated injections of identical amounts of dye-indicator. In 12 studies Lanatoside-C was administered intravenously in doses of 1.2 to 1.4 mg. After the first exercise period no significant difference was noted in either the resting cardiac output or the normal response of the cardiac output to a standard exercise between the control subjects or those given Lanatoside-C. It is not denied, however, that the Lanatoside-C may have altered several factors in conflicting directions to leave the "net" cardiac output response the same. From this experiment it would appear that there is no valid reason for withholding a cardiac glycoside for fear of impairing the circulatory response to a stress comparable to moderate walking exercise.

LEVINSON

Hamlin, R. L., Smith, C. R., and Redding, R. W.: Time-order of Ventricular Activation for Premature Beats in Sheep and Dogs. Am. J. Physiol. **198**: 315 (Feb.), 1960.

The average duration for the sinus QRS complex was 0.035 second for sheep and 0.041 second for dogs. The average prolongation of premature beats was 145 per cent in sheep and 210 per cent in dogs. Spatially, the mean QRS vector for both species was directed coplaner to the median sagittal plane—the sheep being minus 120 degrees at a magnitude of 0.8 mv., and the dogs being at 88 degrees and a magnitude of 1.4 mv. In both species, premature beats from left ventricular foci were directed cephalically; and from right ventricular foci, caudally. It is difficult to explain why premature beats from identical foci in sheep and dog hearts have nearly identical mean spatial QRS vectors, yet the prolongation and magnitude is so much greater in the dog whose heart is less than one half the size of the sheep's. There are several possible explanations for the data: that the activation for premature beats is all muscle fiber to muscle fiber; that the impulse quickly re-enters into the Purkinje system; or that a combination of the two exists. The last explanation is most consistent with anatomic studies describing the more complete penetration of the Purkinje fibers into the epicardium of sheep.

KAYDEN

Jacob, M. I., and Berne, R. M.: Metabolism of Purine Derivatives by the Isolated Cat Heart. Am. J. Physiol. **198**: 322 (Feb.), 1960.

Perfusion of the isolated cat heart with Tyrode's solution containing adenosine, adenosine-8-C^{14}, or adenosine triphosphate induced an increase in coronary blood flow and in the amount of inosine and hypoxanthine in the perfusate compared to the perfusion of Tyrode's solution alone. Perfusion of the cat heart with inosine did not induce coronary vasodilatation. Adenosine deaminase and nucleoside phosphorylase were leached out of the isolated cat-heart preparation during the perfusion process. Adenosine, added to the perfusate collected after one passage through the cat heart, was converted to inosine and hypoxanthine. When the heart was perfused with adenosine-8-C^{14} approximately 50 per cent of the adenosine entered the myocardial cells, where it was trapped as adenine nucleotide; the remainder was recovered in the perfusate as inosine and hypoxanthine. Perfusion of dinitrophenol induced coronary vasodilatation and an increase in the amount of inosine and hypoxanthine recovered in the perfusate. It is postulated that dinitrophenol effects the release of adenosine from the myocardial cells and thereby produces coronary vasodilatation.

KAYDEN

Langen, C. D.: Cardiac Muscle Edema. Hemodynamic Factors Ensuring Adequate Function of the Tissue Flow in the Cardiac Muscle. Cardiol. **36**: 111, 1960.

Edema of the cardiac muscle has attracted very little attention. In beriberi there is real edema of the heart muscle. The electrocardiogram shows no anomalies, parallel to the greater content of tissue fluid, only the P-Q distance is regularly shortened. There are some other rare diseases with edema of the cardiac muscle. The heart is the only organ that by its function regulates its own tissue fluid movements. The problems of tissue fluid movement are discussed.

BRACHFELD

Sarnoff, S. J.: Certain Aspects of the Role of Catecholamines in Circulatory Regulation. Am. J. Cardiol. **5**: 579 (May), 1960.

Studies in dogs of the automatic influences on cardiac contractility are described. Sympathetic activity, induced by stimulating the stellate ganglion or by depressing the carotid sinus, resulted in atrial and ventricular contractions that were briefer and more forceful. Contractility was augmented at all levels of end-diastolic or mean atrial pressure so the whole Starling curve was shifted to the left by sympathetic effects. Parasympathetic activity, induced by stimulating the distal cut end of either vagus nerve or by increasing carotid pressure, caused the ventricle to produce less work at a given mean atrial pressure, and thus the Starling curve was shifted to the right. However, ventricular contractility was not detectably influenced by vagal stimulation when ventricular work production was released to end-diastolic pressure. Atrial systole, which was depressed by vagal action, was found to contribute significantly to ventricular end-diastolic pressure, especially when the latter was low or normal. It was concluded that the central nervous system with its connections to the heart can vary the end-diastolic pressure and myocardial fiber length and can vary the catecholamine stimulus to which ventricular contractility will be proportional.

ROGERS

Sperelakis, N., Hoshiko, T., and Berne, R. M.: Nonsyncytial Nature of Cardiac Muscle: Membrane Resistance of Single Cells. Am. J. Physiol. **198**: 531 (Mar.), 1960.

Previous work has suggested that the myocardium is not a functional syncytium. In the present study of isolated frog ventricle, constant-current pulses were used to estimate the direct current resistance between 2 microelectrodes when both were extracellular, one was intracellular, and both were intracellular. A resistance of 12.4 ± 0.5 megohms was obtained for single cells. This large resistance indicates that the cells are functionally small units. The resistance between 2 cells was about twice that of 1 cell and was independent of the distance between the cells. Hence there were no low-resistance pathways between the cells. The results support the thesis that conduction in the heart does not involve a functional syncytium; rather junctional transmission may occur from cell to cell. Myocardial cells, which had been previously punctured, generally showed a much lower resistance, even though the resting and action potentials were normal.

KAYDEN

Sproule, B. J., Mitchell, J. H., and Miller, W. F.: Cardiopulmonary Physiological Responses to Heavy Exercise in Patients with Anemia. J. Clin. Invest. **39**: 378 (Feb.), 1960.

The cardiopulmonary responses of 9 male patients with various types of anemia were compared with those of a larger number of normal subjects during heavy treadmill exercise. At rest, anemic individuals, by expanding available hemodynamic compensatory mechanisms, were able to handle the delivery of oxygen and the transport of carbon dioxide in relatively adequate fashion. Compensation was achieved by several means, which included an increased level of ventilation and cardiac output, a shift to the right of the oxygen dissociation curves, and an increased desaturation of venous blood which, because of the Haldane effect, augmented carbon dioxide transport. During strenuous exercise, these hemodynamic adjustments were insufficient to prevent a marked depression of both oxygen uptake and carbon dioxide protection in comparison with those found in normal individuals exercising at comparable levels. Despite the evidence for an increase in anerobic-metabolism in anemic subjects, and in spite of the reduced buffering capacity reflected in the resting state by an increased arteriovenous pH difference, the arterial and venous pH was not lower than normal. The absence of a greatly exaggerated arteriovenous pH difference during vigorous exercise suggests that there may be a lag in the release from the tissues of acid metabolites arising from anerobic glycolysis in anemic patients. But these subjects showed no more symptomatic distress than did normal people during these same periods of violent exercise.

KAYDEN

PULMONARY DISEASES

Kabins, S. A., Fridman, J., Neustadt, J., Espinosa, G., and Katz, L. N.: Mechanisms Leading to Lung Edema in Pulmonary Embolization. Am. J. Physiol. **198**: 543 (Mar.), 1960.

A localized pulmonary infarction was produced by injecting a starch suspension into the pulmonary artery wedge position of 1 lung lobe in pentobarbitalized dogs. The effect of 3 so-called antiserotonins on the ensuing pulmonary edema was determined. Edema was inhibited in the nonembolized lobes in 88 per cent of dogs treated with BAS (1-benzyl-2-methyl-5-methoxytryptamine HCl), 45 per cent of those treated with DHE (dihydroergotamine), and 12 per cent of those treated with BOL (2-brom-d-lysergic acid diethylamide). Reasons are given for assuming that the actions of BAS and DHE are due to their antiadrenergic rather than to any

antiserotonin properties that they may have. Serotonin, therefore, has at most a slight role in the formation of pulmonary edema caused by starch emboli. It is postulated that the emboli, by producing an infarct and setting up a reflex mediated through the sympathetic nervous system, cause the release in turn of catecholamines and of histamine, the latter being immediately responsible for the capillary permeability change leading to pulmonary edema.

KAYDEN

RENAL AND ELECTROLYTE EFFECTS ON THE CIRCULATION

Kelly, H. G., Cross, H. C., Turton, M. R., and Hatcher, J. D.: Renal and Cardiovascular Effects Induced by Intravenous Infusion of Magnesium Sulphate. Canad. M. A. J. **82**: 866 (Apr. 23), 1960.

Hypertensive and normotensive subjects were infused intravenously with magnesium sulfate solution, usually 8 Gm. in 250 ml. of physiologic saline in 50 to 80 minutes. Transient vasodilatation resulted as indicated by cutaneous flushing, slightly increased renal plasma flow, and, in most instances, a lowering of blood pressure. The last was more pronounced during faster infusion rates and in hypertensive patients, but even in them there was little associated change in heart rate. Glomerular filtration rate increased only in hypertensive patients. There was a variable rise in plasma magnesium level depending on the infusion rate. The serum sodium, chloride, potassium, and phosphorus values did not change significantly, but there was a fall in serum calcium. The latter was attributed to calcium diuresis promoted by sulfate and was not observed when a magnesium chelate was infused. Renal tubular function was altered to produce increased excretion of magnesium, sodium, chloride, and water—effects that were more pronounced in the normotensive subjects. Potassium excretion was increased in the hypertensive patients but decreased in the normotensive individuals, and no consistent change in phosphorus diuresis was observed.

ROGERS

Muirhead, E. E., Stirman, J. A., and Jones, F.: Renal Autoexplanation and Protection against Renoprival Hypertensive Cardiovascular Disease and Hemolysis. J. Clin. Invest. **39**: 266 (Feb.), 1960.

Bilateral nephrectomy of the dog is associated with the development of hypertension, cardiovascular injury characterized by cardiac necrosis and subsequently fibrosis, and a hemolytic state identified by the shortening of erythrocyte survival time in vivo. The effects of explanations of various portions of the kidneys upon these features of bilateral nephrectomy were studied in the dog. Renal tissue was explanted to the peritoneum and lungs of the same dog. When whole kidney or renal medulla was explanted, certain cells appeared to take hold and proliferate locally. The cells assumed the appearance of tubules in irregular clusters and lacked an organized excretory arrangement. Protection against accelerated hypertension as encountered following bilateral nephrectomy plus a sodium and protein intake was observed following explantation of whole kidney, whole renal medulla, or outer renal medulla derived from 1 kidney followed by removal of the other kidney. The explanted animals received the same amount of sodium and protein as the nephrectomized group. Protection against accelerated hypertension was not afforded by explantation of renal cortex from one kidney followed by removal of the other kidney, or by explantation of the spleen or a portion of the liver followed by renal ablation. Explanted whole kidney, whole renal medulla, and outer renal medulla in the absence of both normal kidneys also afforded protection against the hemolytic state as observed following bilateral nephrectomy. Explanted renal cortex did not protect against hemolysis. It is suggested that the protective function or functions against the hypertensive state and hemolysis appear to be of nonexcretory type and to be mainly within the renal medulla. The nature of this function is unknown.

KAYDEN

RHEUMATIC FEVER

Bland, E. F.: Declining Severity of Rheumatic Fever: A Comparative Study of the Past Four Decades. New England J. Med. **262**: 597 (Mar. 24), 1960.

A long-term study of rheumatic fever is reported concerning the nature and severity of rheumatic fever in recent years as compared to the past. A comparison was made of the first 100 consecutive cases of initial attacks of rheumatic fever admitted to the House of the Good Samaritan in Boston in the years 1921-22, 1930-31, 1940-41, and 1950-51. It was found that during these 4 decades there was a modest decline in the incidence of carditis in terms of residual murmurs from 75 per cent in 1921-22 to 60 per cent in 1950-51; a 2-fold amelioration in the severity of carditis as indicated by heart size; and an 8-fold reduction in mortality rates. In this series the decline in the severity and extent of acute rheumatic fever became most striking toward the end of the 1930-39 decade. Certain

factors that may have contributed to this improvement are discussed. These include the considerable over-all improvement in the standards of living for the poorer classes of urban areas, the increased awareness of the medical profession of the causative role of streptococcal infection in the disease with the institution of general and specific measures for the treatment and prevention of streptococcal infections, and a natural mutation of the disease itself.

SAGALL

Combined Rheumatic Fever Study Group: A Comparison of the Effect of Prednisone and Acetylsalicylic Acid on the Incidence of Residual Rheumatic Heart Disease. New England J. Med. **262:** 895 (May 5), 1960.

A carefully controlled study was undertaken to determine whether in the treatment of acute rheumatic fever prednisone given over a 12-week period was more effective in preventing residual rheumatic heart disease than therapeutic doses of acetylsalicylic acid given for a similar period of time. Fifty-seven patients with their first attack of unequivocal rheumatic fever met the criteria for inclusion. Twenty-nine of these received prednisone, 60 mg. daily in divided doses with gradual reduction during the next 9 weeks for a total of 3 Gm. The remaining 28 patients were given acetylsalicylic acid in a dosage of 50 mg. per pound of body weight in divided doses for 9 weeks, 30 mg. per pound daily in divided doses for 2 weeks and 5 mg. per pound daily for 1 week. Both treatment groups also received penicillin in therapeutic doses for 10 days and prophylactically thereafter. Follow-up observation indicated that prednisone in the dosage employed was not superior to acetylsalicylic acid in preventing residual rheumatic heart disease. The chief action of both medications appeared to be the suppression of the inflammatory reaction caused by rheumatic fever. It also was evident that in many patients prompt and well-controlled suppression of the acute symptoms by these drugs still did not prevent cardiac damage.

SAGALL

ROENTGENOLOGY

Derrick, J. R., Cooley, R. N., Agnew, C. H., and Bermudez, R.: Selective Visceral Arteriography. Surgery **47:** 651 (Apr.), 1960.

A technic for selective visualization of the celiac axis, superior mesenteric artery, and renal arteries is described. The tip of a Lehmann catheter was heated in a curved mold so that the distal 4 to 7 cm. described an arch of 90 to 120 degrees. A thin, flexible, stainless-steel stilette was then introduced to straighten the tip of the catheter. On removal of the stilette the catheter reassumed the molded curve. Subjects with significant arterial insufficiency of the lower extremities were eliminated from study by this technic. After local anesthesia the femoral artery was exposed. If there was any evidence of atherosclerosis, the procedure was terminated. The catheter was introduced into the femoral artery and advanced under fluoroscopic control. When the catheter tip was near the desired orifice, small amounts of contrast medium were rapidly injected and multiple films were taken. This technic was used in 22 instances. In 1 patient a subcutaneous hematoma occurred at the site of artery repair. In another patient a local arterial thrombosis was successfully removed.

SHEPS

Porstmann, W., and Iwig, J.: The Intramural Coronary Artery in the Angiogram. Fortschr. Rontgenstr. **92:** 129 (Feb.), 1960.

During aortic angiography in a 19-year-old patient with aortic stenosis, the ramus descendens of the left coronary artery, which was very well visualized, showed narrowing only during systole. This was shown in serial angiograms taken at the rate of 6 per second. This behavior was attributed to a more or less extensive invagination of a coronary artery branch into the myocardium. This anatomic variant was previously found in 22 per cent of anatomically studied hearts. If only a single coronary angiogram is taken, such a finding could be misinterpreted as due to organic coronary stenosis. This error could be avoided by use of serial films.

LEPESCHKIN

SURGERY AND CARDIOVASCULAR DISEASE

Edwards, C. H., Gordon, N. S., and Rob, C.: The Surgical Treatment of Internal Carotid Artery Occlusion. Quart. J. Med. **29:** 67 (Jan.), 1960.

The present paper assesses the role of reconstructive arterial surgery in the treatment of internal carotid artery thrombosis by a detailed follow-up of a series of 40 patients who had complete or partial occlusion of the internal carotid artery. The commonest symptom was weakness of one side of the body, sometimes recurrent, transient, and increasingly severe. Headache, epileptic fits, and visual disturbances were present in some. Nine showed impairment of intellect; disorders of speech were common as well as homonymous hemianopsia and unilateral upper motor neuron weakness. A bruit over the con-

trolateral eye was heard in 2 patients. Carotid angiography performed in 38 patients showed complete block of the internal carotid artery in 19 patients and partial occlusion in 18. Thirty-two patients underwent operation. It was possible to remove the obstruction in 18 patients, in 14 of whom a partial occlusion and in 2 of whom a complete occlusion had been demonstrated by angiography. In 14 patients it was impossible to re-establish blood-flow. When occlusion of the internal carotid artery was complete, a local or general anesthetic was used; when the occlusion was partial, hypothermia was desirable. Thromboendarterectomy, the simplest procedure, was performed when possible. Carotid occlusion was limited to a maximum of 20 minutes. No anticoagulants were given in the immediate postoperative period. When long-term anticoagulants were used, they were started 48 hours after operation. The best results followed a direct end-to-end anastomosis, though this was technically seldom possible. The next best procedure was a thromboendarterectomy; the insertion of an arterial transplant or venous graft was least satisfactory. The factors that give the most favorable prognosis are a "stuttering" type of onset, a partial arterial stenosis, and the establishment of a satisfactory back flow of blood at operation. These patients are the ones most likely to be free of permanent disability prior to operation. A relatively poor prognosis was noted in patients with a gradual onset suggesting widespread arterial disease.

KURLAND

Gilbert, J. W., Jr., and Morrow, A. G.: Gastrointestinal Bleeding after Cardiovascular Operations in Children. Surgery 47: 685 (Apr.), 1960.

Four children are described who exhibited gastrointestinal bleeding within the first few postoperative days subsequent to cardiovascular surgery. The first indication of this was hematemesis in 1 patient and melena in the remainder. Medical treatment proved effective in 3 instances, but the fourth patient died following perforation and a second exanguinating hemorrhage. The only factor common to all 4 patients was the general nature of the surgical trauma. The nature and occurrence of so-called "stress ulcer" is reviewed.

SHEPS

Kolff, W. J., Effler, D. B., and Groves, L. K.: A Review of Four Dreaded Complications of Open-heart Operations. Brit. M. J. 1: 1149 (Apr. 16), 1960.

The 4 complications reviewed were acidosis, overoxygenation, heart block, and pulmonary defects. Acidosis was most severe 3 or more hours after surgery. It can occur after any type of surgery, but particularly in open-heart surgery, whenever a low cardiac output had been present for a long period of time. The younger the patient the more likely it was to occur. If acidosis is severe, it can cause death unless promptly corrected by the intravenous administration of sodium bicarbonate. It is unlikely that the human organism has a defense mechanism against overoxygenation, though it has not been proved to have a deleterious effect. Heart block can develop when surgery involves the area of the atrioventricular bundle. A pacemaker should be available with every open-heart operation. If heart block occurs during surgery, an electrode should be sewn to the myocardium before closing the chest, even though the heart rate is satisfactory while the patient is on the table. Pulmonary complications can usually be avoided. Apparently pulmonary damage is due to overfilling of the pulmonary vascular bed with blood, leading to capillary damage. Dynamic insufficiency of the left ventricle is the most common cause. However, increased bronchial flow such as occurs in tetralogy and open ductus can also cause difficulties. To prevent pulmonary complications a wide cannula is placed in the left atrium to measure its pressure, and if the pressure rises too high, some blood can be drained from the atrium into the pump oxygenator.

KRAUSE

Mendelsohn, D., Jr., Macdonald, D. W., Nogueira, C., and Kay, E. B.: Anesthesia for Open-heart Surgery: Acquired Valvular Diseases. Current Researches in Anesth. & Analg. 39: 110 (Mar.-Apr.), 1960.

Fifty-eight patients were subjected to operative repair of rheumatic valve disease using the Kay-Cross pump-oxygenator with 2-roller pumps. Convoluted disks increase oxygenation 30 per cent without increasing priming volume or hemolysis. A 25-inch oxygenator containing 115 disks increased oxygenation at higher rates of flow and reduced changes in blood level, which impaired oxygenation and facilitated embolism from foam formation. Monitoring of electrocardiogram, electroencephalogram, arterial and venous pressures, temperature, and oxygen tension of blood leaving the oxygenator has supplemented but not replaced the clinical evaluation of the patient. Flattening of electroencephalographic waves or appearance of delta waves was always evidence of inadequate cerebral circulation, but cerebral embolism was not indicated by this method. Carbon dioxide flow into the oxygenator was adjusted to result in an effluent concentration of

3.8 to 4.2 per cent. Mortality following operation for mitral regurgitation or stenosis was 20 per cent while that following operation on the aortic valve was 80 per cent; the latter operation has therefore been suspended until a prosthetic prefabricated valve becomes available. Ventricular fibrillation appeared following elective cardiac arrest by means of potassium in 8 patients. Chemical defibrillation with 0.05 to 0.2 mg. Isuprel was successful in 4 cases of slow fibrillation in flaccid hearts, including 2 in which repeated attempts at electric defibrillation were unsuccessful; the latter alone was successful in 1 case. Administration of a paralyzing dose of succinyl chloride into the oxygenator prevented a marked drop in arterial oxygen saturation caused by mobilization of desaturated blood resulting from skeletal muscle contraction during electric defibrillation. Direct coronary perfusion during aortic surgery obviated the disadvantages of cardiac arrest and has been successfully used in 8 patients. Cerebral embolism occurred in 8 patients. Air embolism (4 patients) can be prevented by maintaining the mitral valve partially open during the operation, filling the left ventricle completely with blood before the valve is allowed to close, and by keeping the perfusion pressure high. Particulate embolism can be prevented by removing all calcium thrombi or vegetations and flushing the left side of the heart. In all instances, metabolic acidosis occurred rapidly at the onset of bypass, but corrected itself spontaneously immediately following bypass, providing the circulation was adequate.

LEPESCHKIN

Smith, R. M., and Engineer, E. H.: Problems Related to Open-Heart Operations on Children. Part I. Current Researches in Anesth. & Analg. 39: 104 (Mar.-Apr.), 1960.

Of 230 open-heart operations using the DeBakey roller pump and the Kay-Cross disk oxygenator no deaths have been caused by obvious breakdown of the pump-oxygenator. After premedication with morphine, atropine, and pentobarbital, anesthesia was induced with cyclopropane and continued with nitrous oxide and a relaxant (succinylcholine injected as needed intravenously or into the deltoid muscle). Prior to establishment of the bypass, thiopental may be mixed with the priming blood in the pump in order to prevent sudden awakening of the patient when extracorporeal circulation is started. Infants with enlarged hearts should be given only low concentrations of cyclopropane. Heart block occurring during repair of ostium primum and ventricular septal defects has been the primary factor in 15 deaths. On termination of the bypass, ventricular fibrillation may appear, but is usually easily terminated by electric shock. Severe hypotension caused by primary myocardial failure may appear at this time, especially if the operation involves the closing of a shunt. After massage, injection of calcium chloride, 50 per cent glucose and epinephrine, and finally neosynephrine have been tried. The infusion of a solution containing 4 mg. of epinephrine and 1 Gm. of calcium chloride in 100 ml. 5 per cent glucose has been successfully used as long as several days to combat myocardial failure. Continued bleeding could not be attributed to heparin in any of the patients of the series, as evidenced by protamine titration. The platelets were usually reduced in bypass blood, but while the 2 patients with the greatest reduction showed bleeding, the platelet count has not correlated well with bleeding tendency. The most effective therapy is the use of whole blood, drawn immediately before administration.

LEPESCHKIN

UNCOMMON FORMS OF HEART DISEASE

Aldridge, H. E., and Greenwood, W. F.: Myxoma of the Left Atrium. Brit. Heart J. 22: 189 (Apr.), 1960.

Three patients are reported who were thought to have mitral stenosis and who were found at operation to have a myxoma of the left atrium. These 3 patients and 32 additional patients with sufficient clinical details were extensively reviewed. It was concluded that the differentiation between mitral stenosis and left atrial myxoma is usually impossible. The clinical characteristics which might suggest a myxoma are rapid, unremitting downhill course, syncope, or emboli with sinus rhythm.

KALMANSOHN

Catterall, M., and Evans, W.: Myocardial Injury from Therapeutic Irradiation. Brit. Heart J. 22: 168 (Apr.), 1960.

Twenty-six patients with carcinoma of the breast or lung were investigated before and after radiotherapy for evidences of myocardial injury. Careful measurements revealed that the heart received significant irradiation. Pulmonary function tests did not show deterioration in those patients in whom electrocardiographic changes occurred, in contrast to the theory that the lung was more sensitive to irradiation than the heart and that lung damage was present in patients where irradiation has injured the heart. In the group with irradiation of the mediastinum, there were no changes in the post-irradiation electro-

cardiogram; there were no changes in the tracings of the patients with irradiation of the right side of the chest. In all 9 patients with irradiation of the left side of the chest in whom the heart remained in the path of the therapeutic beam, significant electrocardiographic changes followed radiotherapy. The electrocardiographic changes were confined to the T waves; the changes persisted for 4 months in all patients, but disappeared after 12 months in each of the 5 patients followed for that period of time. It was thought that the changes were due to transient myocardial injury.

KALMANSOHN

Garret, G., Hay, W. J., and Rickards, A. G.: Familial Cardiomegaly. J. Clin. Path. **12**: 355 (July), 1959.

The syndrome of familial cardiomegaly first described in 1949 has the essential features of familial incidence of cardiomegaly without obvious cause and a marked tendency to arrhythmia and heart block, with associated palpitation, giddiness, and syncope. Death may be sudden, or rapid due to the development of left ventricular failure. In the electrocardiogram, the QRS complexes are exceptionally wide, and the T waves inverted. Conspicuous myocardial fibrosis and hypertrophy of the remaining muscle fibers are striking pathologic findings. Both the degree of the conduction defect and the prognosis seem to depend on the extent of myocardial fibrosis and cardiac enlargement. This paper presents an example of a family with cardiomegaly, the three affected members dying suddenly. A man aged 30 and his 2 sisters, each at the age of 18, died suddenly, without history of rheumatic fever and previous illnesses. Cases reported may be divided into those in which the muscle hypertrophy was the main or only abnormal finding and those in which hypertrophy was accompanied by widespread fibrosis. Although there are numerous theories of origin, the etiology of the syndrome remains obscure.

MAXWELL

Reimers, H. F.: Calcificant arteriopathy of infants. Ztschr. Kreislaufforsch. **49**: 166 (Feb.), 1960.

A nine-month-old female infant died on the day of admission with signs of cardiac failure, after having had an uneventful history except for lack of appetite. Autopsy showed proliferation of the intima and extensive calcification with giant cell granulomas in the media and intima of the muscular arteries and calcification of the media in the elastic arteries. These changes differed from those of arteriosclerosis, Mönckeberg's calcification of the media, and rheumatic arteritis. The myocardium showed extensive focal muscle necrosis with calcification. Study of 50 cases from the literature showed that death occurred usually before the eighth week, but sometimes as late as the third year of life. The etiology is unknown but some injurious perinatal influence is probably the cause.

LEPESCHKIN

VALVULAR HEART DISEASE

Altland, P. D., Highman, B., and Roshe, J.: Effects of Altitude on Dogs with Valvular Heart Disease. Arch. Path. **68**: 475 (Nov.), 1959.

Normal dogs and dogs with surgically induced aortic (AI) or mitral insufficiency (MI) or both were exposed to 30,000, 32,000, 34,000 and 36,000 ft. simulated altitude in decompression chambers. The lesions did not reduce tolerance to an acute exposure under 34,000 ft. At 34,000 and 36,000 ft., 6 of 19 dogs with valvular lesions died, as against 1 of 15 controls. Death was considered to be caused by respiratory failure. A few fat emboli were found in the lungs of 2 of 5 acutely exposed dogs studied for fat. One AI dog with endocarditis and myocarditis lived only 15 minutes at 30,000 ft. The authors suggest that other severe pathologic lesions may reduce the tolerance to altitude in animals with valvular defects and may also explain the anginal patient's poor tolerance to hypoxia, on the basis of myocardial impairment caused by a deficiency in coronary circulation. Chronic exposure to 30,000 ft. simulated altitude produced similar effects in control animals as in AI dogs and in both were more severe than at 25,000 ft. At 30,000 ft., renal and splenic infarcts, cardiac vegetations, and ulceration of the pylorus occurred. Also demonstrated were increased cellularity of bone marrow, focal endocardial and valvular thickening, visceral engorgement, focal myocardial fibrosis, aortic and occasionally coronary, nonlipid arteriosclerotic lesions, and renal hemosiderosis. One dog showed focal demyelination of the corpus callosum. Another showed softening of the parietal cortex. The author's findings indicate that high-altitude exposures are an important factor in the genesis of arteriosclerotic plaques, probably because of anoxia. These lesions were found in the aortas of very young dogs, varying in character and severity with the number of exposures to high altitude.

MAXWELL

NEWS FROM THE AMERICAN HEART ASSOCIATION

44 East 23rd Street, New York 10, New York

Telephone Gramercy 7-9170

Abstracts of Papers Due May 15 For AHA Scientific Sessions

May 15, 1961, is the deadline for submitting abstracts of papers to be presented at the 34th annual Scientific Sessions of the American Heart Association in Bal Harbour, Florida, October 20-22, 1961.

Papers intended for presentation must be based on original investigative work in the cardiovascular or related fields. Abstracts, in 250 words or less, should include a digest of the results obtained and conclusions reached.

Official forms for submitting abstracts and applications for scientific exhibit space, also due May 15, may be obtained from Richard E. Hurley, M.D., Medical Associate, American Heart Association, 44 East 23rd Street, New York 10, New York. Applications for industrial exhibit space may be obtained from Steven K. Herlitz, Inc., 280 Madison Avenue, New York 16, New York.

Association's Scientific Sessions Will Present Varied Program

A program of varied interest, including six sessions on clinical cardiology and concurrent scientific sessions or programs sponsored by the Association's eight Councils, is being planned for the 34th annual Scientific Sessions of the American Heart Association.

The sessions are scheduled to be held in the Hotel Americana, Bal Harbour, Florida, from Friday, October 20, through Sunday, October 22, 1961.

Also included in the program will be a session for nurses, an all-day showing of cardiovascular films with commentary by the author or other authority on the subject, and various lectures, panels and symposia.

Following the AHA Scientific Sessions, Cardiological Sessions under sponsorship of the Puerto Rican Heart Association will be held in San Juan, Puerto Rico on October 26-27.

May 15 is Abstracts Deadline For Arteriosclerosis Council Meeting

The Council on Arteriosclerosis of the American Heart Association will hold its Annual Meeting October 18-20 at the Hotel Balmoral, Bal Harbour, Florida, immediately preceding the AHA annual Scientific Sessions.

May 15 is the deadline for submitting abstracts of papers to be presented at the Council meeting. All interested individuals, whether or not they are Council members, are invited to submit abstracts and to attend the Council sessions. Official forms for submitting abstracts, which are to be limited to 250 words, are available from Jeremiah Stamler, M.D., Chicago Board of Health, 54 West Hubbard Street, Chicago 10, Illinois, or from the American Heart Association.

Leaflet on Innocent Heart Murmurs Issued for Physician Distribution

A new leaflet which may be used by physicians to help them allay the unwarranted fears of parents whose children have

functional heart murmurs has been issued by the Association and its affiliates.

Written in simple lay terms, the four-page leaflet emphasizes the harmlessness of innocent murmurs in young children and explains why periodic reexamination in such cases is sometimes necessary. Entitled "Innocent Heart Murmurs in Children," it is available to physicians from their local Heart Associations or the American Heart Association.

Seminar on Vascular Systems Scheduled for October 17-19

An International Seminar on the Vascular Systems has been scheduled for October 17-19, 1961, at the Beau Rivage Hotel, Miami Beach, Florida, under auspices of the Heart Association of Greater Miami, University of Miami School of Medicine, Florida Heart Association and University of Florida Medical School.

The Seminar's program will be directed primarily to physiologists, academic clinicians, cardiologists with teaching interests and workers in related fields of circulatory dynamics and pathology. Further information may be obtained from John B. Liebler, M.D., Chairman of the Seminar Committee, Heart Association of Greater Miami, 253 S.W. Eighth Street, Miami 36, Florida.

AHA-ACC Negotiations Suspended

At intervals during the past two years, a Liaison Committee of the American Heart Association and the American College of Cardiology has discussed conditions of possible affiliation of the College with the Association. During this period, the Association has sponsored a Scientific Session at the Annual Meeting of the College, and the College, in lieu of its Interim Meeting, has joined with the Association in the sponsorship of a Scientific Session and Fireside Conferences at the Association's Annual Meeting.

Unfortunately, these efforts to effect affiliation of the College with the Association have not proved successful. If problems relating to the proposed conditions of affiliation should be solved, negotiations between the Association and the College will be resumed.

Meetings Calendar

May 16-20: American College of Cardiology, New York. Philip Reichert, 350 Fifth Ave., New York 1, New York.

May 31-June 2: Canadian Federation of Biological Societies, Guelph, Ontario. E. H. Bensley, 1650 Cedar Ave., Montreal 25, Canada.

June 22-26: American College of Chest Physicians, New York. Murray Kornfeld, 112 E. Chestnut St., Chicago 11, Illinois.

June 23-25: American College of Angiology, New York. Alfred Halpern, 11 Hampton Court, Great Neck, New York.

June 25: Society for Vascular Surgery, New York. George H. Yeager, 314 Medical Arts Bldg., Baltimore 1, Maryland.

June 25-30: American Medical Association, Annual Meeting, New York. F. J. L. Blasingame, 535 N. Dearborn, Chicago 10, Illinois.

July 1-4: International College of Surgeons, New England Regional Meeting, Chatham, Massachusetts. M. L. Brodny, 4646 N. Marine Dr., Chicago 40, Illinois.

July 10-24: International Conference on Medical Electronics, New York. L. E. Flory, David Sarnoff Research Center, Princeton, New Jersey.

August 7-10: National Medical Association, New York. John T. Givens, 1108 Church St., Norfolk, Virginia.

August 27-September 1: American Congress of Physical Medicine and Rehabilitation, Cleveland. Dorothea C. Augustin, 30 N. Michigan, Chicago 2, Illinois.

September 26-29: American Roentgen Ray Society, Miami Beach. C. A. Good, Mayo Clinic, Rochester, Minnesota.

October 2-6: American College of Surgeons, Chicago. W. E. Adams, 40 East Erie St., Chicago 11, Illinois.

October 3-4: Congress on Occupational Health, Denver. Council on Occupational Health, American Medical Association, 535 N. Dearborn, Chicago 10, Illinois.

October 14-20: International Congress of Neurosurgery, Washington, D.C. Bronson S. Ray, 525 E. 68th Street, New York 21, New York.

October 17-19: International Seminar on Vascular Systems, Miami Beach. John B. Liebler, Heart Association of Greater Miami, 253 S.W. 8th St., Miami 36, Florida.

October 20-24: American Heart Association, Annual Meeting and Scientific Sessions (October 20-22), Bal Harbour, Florida. American Heart Association, 44 East 23rd St., New York 10, New York.

November 13-17: American Public Health Asso-

ciation, Detroit. Berwin F. Mattison, 1790 Broadway, New York 19, New York.

November 16-18: International Symposium "Etiology of Myocardial Infarction," Detroit. Thomas N. James, Henry Ford Hospital, Detroit 2, Michigan.

November 27-30: American Medical Association, Clinical Meeting, Denver. F. J. L. Blasingame, 535 N. Dearborn, Chicago 10, Illinois.

Abroad

June 2-5: Latin-American Congress of Physical Medicine, Lisbon. C. L. deVictoria, 245 E. 17th St., New York, N. Y.

June 3-15: International Medical-Surgical Meetings, Turin, Italy. Minerva Medica, Corao Bramante 85, Turin.

August 22-25: International Pharmacological Meeting (First) Stockholm. A. Wretlind, Karolinska Institutet, Stockholm 60, Sweden.

August 28-September 2: European Society of Haematology, Vienna. H. Fleischhacker, Wien IX, Frankgasse 8, Billrothhaus, Austria.

September 3-7: International Congress on Rheumatology, Rome. Prof. C. B. Ballabio, Clinica Medica Generale, Via F. Sforza 35, Milano, Italy.

September 3-10: Inter-American Congress of Radiology, Sao Paulo. W. Bomfim-Pontes, Rua Cesario Motta, No. 112, Sao Paulo, Brazil.

September 4-9: International Congress of Angiology, Prague. Prof. Z. Reinis, IVth Medical Clinic, Praha 2/499, Czechoslovakia.

September 6-12: International Congress of Human Genetics, Rome. Luigi Gedda, 5 Piazza Galeno, Rome, Italy.

September 7-9: International Cardiovascular Society, Vth Congress, Dublin. H. Haimovici, 715 Park Ave., New York 21, New York.

September 10-15: International Neurological Congress, Rome. G. Alema, Vialo Universita 30, Rome, Italy.

1962

October 7-13: Fourth World Congress of Cardiology, Mexico City. I. Costero, Secretary General, Ave. Cuauhtemoc 300, Mexico, D.F.

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